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ORIGINAL ARTICLES

REMODELING MEDICAL EDUCATION

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Professional service has its techniques, but it should not be a technology—it takes a man, not a machine, to understand a man.—Raymond B. Allen.

THE position of science in the modern world has been aptly compared to that of the church in medieval times. Just as the manifestos of the church were then accepted without question, today the pronouncement that "it has been scientifically proved" is sufficient authority for the general public.

In somewhat similar vein, a statement to the effect that medical education has not kept pace with the rapid changes in medical practice is accepted without critical analysis by many physicians and taken to mean that a sweeping revision of the entire medical curriculum is indicated. Is this position justifiable? Should we choose a new site, lay a new foundation and erect a new edifice to house medical education? Or is the old building structurally so sound that it would be better to modernize it from within? Can additions be made without spoiling the "lines" which are of such symmetry that they have been admired throughout the world?

This is a question of great importance to which I will not attempt to give a categorical answer. On the other hand, there is no doubt that the present building is in urgent need of a thorough house cleaning, and that some remodeling is in order.

It is the objective of this paper to offer suggestions for certain simple changes and additions which are needed now.

STUDENT BODY

We must face the fact that there is a wide variation in the level of instruction among the approximately 800 approved colleges in the United States. This is clearly attested by the great difference in the mean scores of students from the different colleges on the Medical College Admission Test. On a scale in which 800 is the highest possible score, the mean "index of general ability" grade for all students from the college with the

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highest standing in a recent year was 638, as compared with that of 314 from the college with the lowest standing.

Since medical schools tend to draw most of their students regularly from the same group of colleges, it therefore seems likely that wide differences in the caliber of students should appear among the various schools. It is my impression, based on conversations with students, on attendance at student conferences, and on the opinion of instructors who have taught at several schools, that there is a considerable difference in the general level of preparation and especially of intellectual maturity of the students in some schools of medicine, as compared with certain other schools. It is my belief that this variation is fostered by the present epidemic of restriction of admissions to the home state which is sweeping the medical schools of the country and that in this time of great demand for medical education, this difference could be wiped out in large measure.

Throughout the country as a whole for the class entering in 1949, there were about 14.4 applications and 3.5 applicants for each admission to medical school. This does not mean, however, that the best 28% of all applicants were necessarily admitted, because there are many schools with fewer than 5 applications for each opening and the ratio varies all the way from 52:1 down to 1.6:1.[1] Meanwhile, the schools with lower ratios are the very ones which will obtain practically all their students from colleges in the home state. With these limitations in choice, it would be almost impossible for school "X" with fewer than 5 applicants per place, chiefly from graduates of less than 10 approved colleges in that state, to select as strong a group of students as school "Y" with over 20 applicants for each opening and actually admitting students from 50 different colleges.

It has been suggested that medical schools now restricting their applications to residents of their own state might make reciprocal agreements with medical schools in other states, for the acceptance of a certain number of residents from those states. This should help to correct a condition which is not now operating to the best interests of the medical profession at large.

Finances

Restriction of admissions to residents of the home state has resulted in significant reduction in the number of medical students enrolled from certain states without medical schools.[2] As a result, several states which do not have the financial resources and hospital facilities to support a medical school properly have been tempted to establish the same. Meanwhile, many medical schools already in existence are in great financial difficulties, and the greatest single impediment to improving their educational standards lies in the lack of funds to initiate the needed changes. A plan by which both of these conditions might be ameliorated is suggested herewith.

A state without a medical school could negotiate agreements under which certain schools would accept each year a fixed number of applicants who were residents of the state in question. The state would then pay to the school an agreed sum per student, the amount being set at a level which would largely reimburse the school for the actual cost of education over and above the tuition fee. Placing this figure arbitrarily at $2,000 and assuming that the state should elect to educate a maximum of 200 students in any given year, the cost to the state would be $400,000. In a study made for the state of Florida, Lippard[3] estimated the cost of establishing a medical school at about $19,000,000 and the annual cost of operation at $2,250,000 if hospital construction and operating costs were included. (Excluding hospital costs the respective figures were estimated to be

$9,000,000 and $800,000.) The saving to the hypothetic state is apparent. Meanwhile there are undoubtedly many medical schools which would be very happy to accept 10 new students each year from a given state if after the fourth year this would add $80,000 to their income over and above the tuition fees of these students.

To the above plan, if desired, could be added an agreement made between state and student for a certain number of years of practice within the state after the completion of training. In addition, tuition scholarships could be established as now provided in Pennsylvania, where each state senator can give three full tuition scholarships each year to students who are admitted to certain institutions.

The Faculty

Our present preoccupation with research has rendered it extremely difficult for a faculty member whose interest and talent lie primarily in teaching to obtain advancement to the higher ranks. Meanwhile, it is fully recognized that research and teaching interest and ability do not necessarily go hand in hand. The result is not always happy from the standpoint of the student and the teaching program.

The preceding statement does not apply with equal force to preclinical and clinical departments. On the other hand, it seems even less well understood that a successful practitioner is not necessarily a good teacher, and that he is not always the best person to head a department. The worst fault lies in the apparent belief that any reasonably successful specialist is perforce capable of teaching his subject. Not infrequently some young specialist in the community is selected and put in charge of a large portion of the teaching program, without reference to his teaching ability or experience, or indeed to his real interest. Sometimes he turns in a splendid performance, at others the result is most unfortunate. Meanwhile there are often a number of able, well-trained younger staff members in other schools who would be available.

The frequency of such fortuitous selection of teaching staff might well be lessened by the establishment of a central registry for medical teachers, as suggested by Lippard.[4] A registry of this sort could operate under the auspices of the Association of American Medical Colleges, or of the Council on Medical Education and Hospitals of the American Medical Association. It could give information concerning both vacancies and available candidates in an entirely ethical and dignified manner and without loss of freedom of action to the schools.

The Curriculum

Discussions of curricula are apt to revolve about the number of hours assigned to different subjects, the division of time among the various forms of teaching, and similar problems largely administrative in nature. We are prone to forget that these matters are of small importance compared with what passes between instructor and student. Santayana wrote (*Character and Opinion in the U.S.A.*): "Teachers and pupils seemed animals of different species, useful and well disposed toward each other, like a cow and a milkmaid; periodic contributions could pass between them, but not conversation." There are indications that this pungent observation still carries a punch that hurts.

Lectures.—Lectures in the clinical years have been discontinued entirely in a few schools, and have become of greatly lessened importance in many others. In some schools lectures are designed primarily to bring out material not readily found in ordinary texts, or to correlate information on certain topics. On the contrary, in many instances, lectures

are merely a recital of what can be read, and is usually better said in any good text. In some cases this results in an exercise so dull that it is ignored by a considerable proportion of the students, either by absence, or if attendance is required, by sleeping, daydreaming or frankly reading some other material.

Amphitheatre Clinics.—By and large, amphitheatre clinics are in far greater favor with students than regularly scheduled lectures. In general, they are handled with more uniform success than any other teaching exercise. The chief shortcoming is failure to have the students participate actively.

Clinical Conferences.—There is wide divergence in the mode of procedure in clinical conferences. In some schools they are conducted almost entirely by the students themselves, the instructor acting merely as a moderator, holding the discussion to the subject and pointing out flaws. In view of the general acceptance of the adage that "the best way to learn is to teach," it is difficult to understand why there is not wider application of this principle. The clinical conference presents an ideal opportunity to exploit this method of instruction. Under the plan in general use, the cases to be shown are assigned sufficiently in advance to give the students in charge of them an opportunity for adequate preparation. Instructors who are not familiar with this method of teaching will be surprised at the excellence of the presentations of many students. They may also be discouraged by the ineptness of others. With experience, however, many of the latter will show great improvement. Incidentally, the method offers an excellent opportunity to evaluate both factual knowledge and mental processes of the students.

In other forms of clinical conference the instructor may lead a discussion in which staff members and students join. Many of these sessions are stimulating and informative.

In other cases the instructor mistakenly interprets a conference as an exercise in which he is expected to do all the talking and the result is simply a didactic lecture to a small group. All too often such instructors take the attitude that since the group is small, no preparation is required. In addition, such conferences are frequently held in rooms totally unsuited to the purpose. Under such conditions it would be better to schedule a formal didactic lecture for the class as a whole and hold it in suitable quarters.

Seminars.—Seminars, like clinical conferences, represent an excellent and too frequently neglected opportunity for student participation. Here they may give before a larger group formal papers to which they have devoted careful preparation. These seminars may be conducted in the manner of standard medical meetings, or by a panel of students, one of whom acts as moderator.

Ward Rounds.—Ward rounds represent probably the oldest form of bedside teaching. Their quality varies from utter boredom to an unforgettable experience. In them the real teacher has an opportunity to develop his own technic and to show his skill.

Three types of ward rounds exemplify the worst abuses to which this form of teaching is subject: (1) "Rounds on roller skates," in which even the fleetest-footed student can catch only an occasional phrase thrown out by the "attending" as he flits from bed to bed; (2) "Business rounds" of the type in which the students merely trail the attendant and resident who hold private conversations regarding immediate details of the patients' care; (3) "Lecture rounds," in which the physician delivers a sermon-length discourse, no matter how learned, to a group of stand-weary students in the center of a ward or corridor or whatever location is most subject to interruption by ward activities and noise.

To the above major abuses might be added, for good measure, a few other common

faults: Sections too large to handle on walking rounds, lack of familiarity with the cases on part of instructor and students alike, use of patients already thoroughly discussed by another instructor, failure to demonstrate physical findings to the students, failure to have x-ray plates available and, last and most important, failure to have the students play an active role. If the student is expected to work up his case thoroughly and follow its progress, he must then be given a chance at ward rounds to take part in the discussion; otherwise he will lose interest.

The Inpatient Clerkship.—In practically all schools, clinical teaching is built about the clerkship, which presumptively is a period during which the student learns through the actual handling of patients. In practice, the clerkship may consist of an invaluable experience during which the primary duty of the student is toward his patient, when regardless of other classes he is called at the time of admission, takes the history personally from the patient or attendant, performs a physical examination, records these findings in a suitable manner and has them checked by someone more advanced in knowledge than himself, performs such laboratory procedures as are suitable for him to do, suggests other procedures, offers his ideas of treatment in specific form, observes treatment which is carried out, follows the course of the patient throughout the latter's stay or the duration of his own clerkship, presents his case at ward rounds, conference or amphitheatre clinic, knows of the plans for after care and follow-up.

In practice also, the clerkship may consist of certain fixed hours of the day during which a group of students arrive at the ward, are assigned cases for physical examination and perform the same, may or may not have their findings checked, read the histories and physical examinations on the chart, assemble with the group and hear one or two cases discussed by the instructor. The student has no responsibility for the patient, does not take a history or see him on admission, does not follow the patient's course. Such a procedure is a "clerkship" in name only.

The Outpatient Clerkship.—The main purposes of outpatient teaching are: (1) To give the student an opportunity to become familiar with those medical conditions which present themselves in office practice; (2) to compress history, physical examination and laboratory procedures into a reasonable space of time; (3) under supervision to diagnose, treat or make suitable disposition of the patient, and to follow him through successive visits. It is easy to see the possibilities and pitfalls of this service. The common faults lie in lack of adequate supervision and in misguided supervision. In the former, the student, left almost entirely to his own devices, is asked to assume a responsibility for which he is not ready. In the latter, the instructor fails to assist the student in establishing and maintaining a proper physician-patient relationship by his attitude and remarks. The instructor should assume the role of a consultant with a medical colleague and all discussion concerning the patient and his disease should be conducted out of earshot of the latter.

Two other common faults are administrative. No effort is made to see that return visits are scheduled with the same student. Again, no record is maintained of the type of cases seen by an individual student, hence there is no diversification of diseases.

Attendance—Compulsory or Voluntary

Emphasis on student participation largely solves the vexing question of whether attendance shall be compulsory or voluntary. There is no doubt that compulsion results in the attendance of some students who gain little or nothing personally and whose

presence is a detriment to the rest of the group. On the other hand, no matter how carefully students may be selected or how high may be the general esprit of the class, there will always be some who need a stimulant to overcome an indisposition to early rising or a disposition toward procrastination. Once present, many of these students will benefit.

Some evidence of what may occur when the importance of attendance is strongly deemphasized, is offered by the following observation made at a school where this philosophy is followed. From 9 to 10 a.m. there was scheduled a clinical conference for the pediatric section of 12 students. The conference was well conducted by a junior staff member who had clearly put a great deal of time and effort into preparation. Four students were present. At 12 o'clock that same day, a deservedly popular member of the upper staff held ward rounds for this same section. There were 14 students present.

It is believed that the plan of complete indifference to student attendance will work well for a large proportion of students in the most carefully selected groups, for a variable percentage of all groups; but that in every group there will be a number who suffer from it. In the final analysis our responsibility lies not in the training of a few star performers, but in guaranteeing that every graduate is qualified to practice medicine.

Needed Additions

In these simple comments on the practical aspects of medical education, emphasis has been placed upon errors of commission rather than those of omission. What are the most glaring deficiencies?

On admission, most medical students are inclined to relate medicine directly to the care of people. During the preclinical years, in addition to imparting factual information, instructors must teach scientific method. That they are largely successful in this dual obligation is no small accomplishment. However, there is but slight attempt to relate this new-found knowledge to living man. There is little or no contact with patients. As a result, the student enters his third year thinking in terms of disease entities.

During the clinical years attention has not been focussed on the patient as an individual who deviates from the normal because of the disease from which he suffers. The interplay of all the forces of family, environment, economics, and fear upon this individual, who is abnormally susceptible because of his illness, is not emphasized to the student. Correction of this fault is rendered difficult by the inevitable use of highly specialized instructors. The natural concern of this group with the details of their own specialty tends to fix the attention of the student even more firmly on the disease than on the patient as a whole.

In a number of schools efforts are being made to point out to the student the clinical application of knowledge being gained in basic science courses, to make him aware of the importance of social factors in the cause of disease and in medical care, and to keep alive his interest in the patient as a person from the very beginning of his medical training. Specific examples of these efforts are not hard to find. I will take the liberty of citing those which are being made at Pennsylvania, with no claim that they illustrate the best examples, nor that they are necessarily original; they are used simply because they represent those attempts with which I am personally most familiar.

An Orientation Course is given to the entering class during the week preceding the formal opening of school. The purpose of this course is fourfold: 1. To familiarize the students with their surroundings. 2. To bridge the gap between college and medical school

by pointing out the differences in the methods of instruction. 3. To indicate the relation of first year courses to medicine as a whole. 4. To present a bird's eye view of their entire medical curriculum.

A course of Introduction to Clinical Medicine is offered early in the first year. In small groups, students see a hospital in operation. They visit wards and admitting services; anesthesia, operating and recovery rooms. They see a patient in shock, in coma. They are given some practical instruction in first aid procedures. This course has been highly successful.

An elective Family Advisor Group is formed among first year students. Each student is assigned a family known to the social service department. The families chosen are habitual attendants at outpatient clinics of the hospital, usually have several small children, or include one member with a chronic disease such as diabetes or rheumatic fever. The student follows the medical adventures of this family throughout his four years in medical school. Space does not permit further elaboration, but the possibilities in this program are obvious.

The method and intent of Correlation Clinics, held throughout the first year and in subsequent years, are too well known to require discussion.

Later in the course the importance of social and environmental factors is again stressed by home visits and conferences with social workers and visiting nurses.

At the end of the third year, a summer session of six weeks offers as an elective preceptorships with practicing physicians. The possibilities and limitations of this training have been discussed fully elsewhere.

It should be clearly understood that the introduction of these specific courses is in no way intended to lessen the emphasis on social medicine in the daily teaching on the clinical clerkship, the importance of which has been noted by Poncher and Richmond.[5] On the contrary, it is hoped that the sum total effect of the courses outlined will be to make the students themselves aware of, and interested in, these factors in their patients, and lead them to seek more guidance from social service workers and instructors.

A "Strong" Medical School

What distinguishes a "strong" school of medicine?

First, it must have a student body carefully selected on the basis of merit from colleges of high standing.

Second, the budget of the school must be large enough to provide an adequate staff.

Third, the administration must establish a schedule which minimizes waste effort by the assignment of blocks of time to the several departments. The administration must be mindful of all factors which affect student morale. It should have a lively interest in the teaching program.

Fourth, the faculty of the basic medical science departments must include members whose interest lies in teaching as well as in research. The lack of either spells mediocrity for the curriculum. The heads of clinical departments must be chosen for their ability to organize and direct a department in which patient care, teaching and research each receive due attention. They, and the heads of subdepartments, must not be selected on the basis of their ability to fill private beds in the hospital. There must be a sufficient number of full-time clinical staff members to carry the basic teaching load.

Fifth, the courses in basic medical science must be so presented that the student leaves

them with a clear understanding of the structure and function of the human body and the relevancy of this information to the practice of medicine. Courses which overemphasize the accumulation of detailed factual knowledge become merely "the rough" which must be endured before reaching "the fairway" of the clinical years.

If the clerkship is the frame into which teaching in the clinical years must fit, then the patient is the canvas upon which the painting will be made, and the student is the artist in training. The best results can be attained only by personal work of the student with the counsel and assistance of the teacher. Upon this concept rests the entire structure of clinical teaching, and the greater the departure, the less satisfactory is the result.

Medical Education Meetings

The interchange of scientific information and ideas through the medium of medical society meetings is a firmly established custom. In recent years discussion of sociopolitical questions in similar meetings has greatly increased. The annual meeting of the Association of American Medical Colleges is the sole organized forum in the United States for consideration of the problems of medical education. This meeting is attended by only a very small proportion of the heads of active teaching departments.

During the survey of pediatric education conducted under the aegis of the American Academy of Pediatrics, regional conferences were held with the heads of pediatric departments throughout the country. A second series of similar meetings was sponsored by the Academy's Committee for the Improvement of Child Health. Invariably the opinion has been voiced by those in attendance that a mechanism should be evolved to establish national meetings on pediatric education at regular intervals. If this is not undertaken by the American Academy of Pediatrics, other means should be found to maintain the effective enthusiasm evinced by pediatric educators.

Meetings whose primary function is consideration of the problems of medical education by those actively engaged in teaching should be established on a firm basis. Such meetings should afford an opportunity for exchange of views on both an intradepartmental and interdepartmental basis. Pediatricians should continue with their own conferences on education, pending the development of a more comprehensive plan involving other departments.

The recent Report of the Medical Curriculum Committee of the British Medical Association closes with the following apt quotation from Thomas Carlyle:

> ". . . Hadst thou not Greek enough to understand thus much: The end of Man is an Action and not a Thought, though it were the noblest?"—*Sartor Resartus*

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SPANISH ABSTRACT

Renovacion de la Educacion Medica

El presente articulo señala la importancia de realizar ciertos cambios en la estructura del curriculum medico y en los metodos actuales de enseñanza. Se destaca el hecho de que los estudiantes de medicina deben participar activamente en los programas de enseñanza para asi obtener el maximo beneficio. El autor describe en detalle las formas en que este beneficio puede ser obtenido con los varios metodos de enseñanza y señala las faltas comunes de los mismos.

El autor dedica gran atencion a la supervision adecuada de los estudiantes en la consulta externa y en la sala de servicio.

Se discute la question de la asistencia obligatoria o voluntaria; sugiriendose como solucion evitar los dos extremos.

Se señala el fracaso de la educacion medica en mantener el paciente como un individuo en relacion al estudiante, asi como de los esfuerzos realizados para corregir esta falta en la escuela del autor.

Las caracteristicas que distinguen una escuela de medicina "fuerte" (strong) son descritas en una sección de este trabajo.

Este articulo termina llamando la atencion del papel importante de las reuniones de las sociedades medicas en el intercambio de informacion cientifica, señalando al mismo tiempo la falta de uso de este metodo en los Estados Unidos cuando se consideran problemas medicos educacionales. Se sugiere que los pediatras continuen realizando las series de conferencias regionales conducidas por los jefes de pediatria, las cuales fueron instituidas durante "el survey" de educacion pediatrica conducido por la American Academy de Pediatrics en el año 1947.

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POSSIBILITIES OF SPECIFIC PREVENTION AND TREATMENT OF POLIOMYELITIS

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IN ATTEMPTING to make a complete review of the current literature on the subject of "specific" poliomyelitis control, I was struck by the divergencies in opinion which have been expressed within just the last few months. As an example, Dr. A. W. Downie, Professor of Bacteriology, University of Liverpool, writes, "No effective means of passive or active immunization are at present available. Latent infections so greatly outnumber clinical cases during outbreaks that general immunization, even if possible, would not appear to be a practicable proposition."[1] Dr. Howard A. Howe of the Johns Hopkins School of Public Health writes, "The logical point at which to break the chain of infections is not by attempting to reduce exposure but rather to control infection by increasing immunity."[2] He then discusses the next steps to be taken in developing a vaccine.

In a paper on the immunity of poliomyelitis which I gave a few months ago, I summarized, in respect to vaccination, "Then from the standpoint of danger, necessity of repeated administration, multiplicity of immunologic types, exorbitant cost, insurmountable logistics and difficulty in selection of susceptibles who need vaccination, it all appears to add up to an impractical and seemingly impossible undertaking."[3] I then cautiously left the door open for retreat in case new developments of an unpredictable nature should appear.

Most recently, Dr. Harry M. Weaver, Research Director of the National Foundation for Infantile Paralysis, states in a recent issue of *Hygeia,* "So, too, it may be possible ultimately to produce a vaccine or a preventive drug against the poliomyelitis virus. This approach at present seems to offer the greatest hope for the conquest of the disease. . . . For the first time in research on poliomyelitis there is good scientific evidence that a vaccine against human poliomyelitis may be developed."[4]

These divergent opinions, of which only a few have been quoted, indicate that a careful objective review of this problem is in order. This review has been made, but only a brief summary of the findings can be presented here. Immunization of the passive type will be considered first, then, more briefly, active immunization, or vaccination and finally, even more briefly, chemo- or antibiotic therapy and prophylaxis.

PASSIVE IMMUNIZATION

The possibility of passively protecting monkeys and mice by serum against an intracerebral challenge of virus has been repeatedly demonstrated.[5–8] Intracerebral inocula-

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tion represents a very severe form of challenge, and protection can usually be demonstrated only when relatively few MLD of virus are given. The serum must be given before or soon after the virus, or at least before signs of illness appear. In most instances a serum from a heterologous species of animal has been employed and the duration of immunity under these circumstances is usually for a period of less than three weeks. Large doses of serum are essential. More recently, gamma globulin from pooled adult plasma has been shown to contain a greater concentration of antibodies to the Lansing strain, and presumably to others as well. The concentration is estimated at from 10 to 16[9] or from 18 to 25 times that of whole plasma.[10,11] When given intraperitoneally it will protect mice and monkeys against an intracerebral inoculation of virus.[12] Gamma globulin promises to be a much more effective and readily available agent than any product used previously.

Howe and Bodian[13] planned one experiment in an attempt to more nearly approach their concept of normal human infection. They employed six chimpanzees. Large doses of virus-containing fecal extract were given by stomach tube and feces were rubbed into the tongue and cheeks. As a prophylactic agent, three of the chimpanzees were given large amounts of specific hyperimmune monkey serum which had been prepared by immunizing monkeys with the virus employed in this experiment. The other three chimpanzees served as untreated controls. None of the animals in either group developed paralysis but all excreted virus in their stools for several weeks. Since in man we are interested principally in preventing paralysis, this experiment does not answer the immediate question—the effect of serum on preventing paralysis—but it does illustrate another important point to be noted later, serum did not interfere with infection. There is much information to indicate that presumably immune adults and older children when exposed to a case in the same family quite regularly become infected and then shed virus for weeks. During this infection they usually remain relatively symptom free.[14–20] Specific immunity, though presumably not preventing infection, probably plays a role in preventing clinical disease and paralysis in some of these infected persons. This is similar to what is recognized as occurring in diphtheria and streptococcal infections.

Very few experiments on the passive immunization of man have been reported. Most of these have been performed with adult human whole blood. The largest was reported by Henry and Johnson[21] and by Stokes, Wolman, Carpenter and Margolis.[22] These reports dealt with Philadelphia, where a large scale immunization of children was attempted in the epidemic of 1932. Over 2,000 children were injected, most of them receiving 60 cc. of whole adult blood from one parent. It was impossible to make a satisfactory statistical analysis of the results in the injected group and in the rest of the population, but the authors felt that the results were very encouraging and recommended further trials. Previous to this experiment, Davide[23] in Sweden had used convalescent serum in a small scale experiment. Park[24] in New York had used either convalescent serum or whole blood from parents, and concomitantly with the 1932 Philadelphia trial,[25] in Bradford, Pa., 1,300 normal children were given 15 to 20 cc. of whole blood. In all three instances the investigators were impressed with the effectiveness of the measures employed, but a satisfactory statistical appraisal cannot be made of any of these.

The most recent report describes an unplanned small scale test of gamma globulin.[26] In the Houston, Texas, outbreak of 1948 many pediatricians followed the example of a few and recommended prophylactic gamma globulin inoculations for the children under their regular care. Bloxsom,[26] by use of questionnaires, summarized their experi-

ence. Obviously, since there were no controls no valid conclusions can be drawn. However, here again, the results followed a pattern such as would be expected should the antibody concentrate have a protective effect. Reports were received, regarding 806 nonsiblings of patients and 35 siblings who were injected with various doses of gamma globulin (average 2.0 cc.) during the outbreak. Four cases occurred among those inoculated. Their onsets were after the following interval in days after injection: 1, 2, 3 and 42. The failures of 1, 2 and 3 days (all siblings of patients) we can certainly attribute to injection too late in the incubation period. Forty-two days (a nonsibling) could well represent an exposure after the level of antibody had fallen to an inadequate level. The report did not state whether the cases were nonparalytic or paralytic, severe or mild.

It should be noted that the gamma globulin or equivalent used in all these reported tests in man averaged 2.0 cc. or less.

Before discussing the appropriateness of a human trial with gamma globulin, let us consider certain pertinent basic immunologic problems.

1. Does antibody play a direct role in the protection of man against clinical disease? Does it present a barrier to the invasion of the central nervous system tissue? Unfortunately, this question cannot be completely answered but there is much suggestive evidence that it does, though most of this comes from experiments performed on laboratory animals, and from parallels with other virus infections. We do finally know, through very recent experiments, that antibody to the specific infecting strain of virus does develop during the course of the disease.[27,28] This presumably plays a protective immunologic role in subsequent infections.

2. Would prophylactic serum completely prevent infection as it does when given in suitable dosage prior to infection with rubeola, and thus only postpone infection to a later year when the risk of paralysis may be greater? Furthermore, would the presence of a large number of artificially immunized persons in a community reduce the dissemination of virus and postpone the age of infection for even the nonimmunized? These are questions of grave importance and, previously, believing the answers to be yes, I have always advised against mass serum prophylaxis, except in special cases, as advised in its use for rubeola. In view of recent developments, however, my opinions are much less certain.

One of these recent developments is a relatively radical hypothesis on the fundamental immunology of poliomyelitis which I have partially developed in two previous papers.[3,29] In one of these,[3] I discussed in some detail the epidemiologic history of Guam during a series of recent outbreaks of communicable diseases. Guam is sufficiently isolated and small so that rubeola, epidemic parotitis, pertussis and varicella have died out repeatedly in its population. At varying intervals, when reintroduced, the agents producing these diseases have given rise to large epidemics. The only record of a possible poliomyelitis outbreak on Guam was in 1899[30] and this affected age groups from 15 years to 50 years. Since then, although the American community has been subjected to at least one outbreak, the Guamanians have not suffered from the paralytic disease. Yet, from serum collections from natives, which I made one year previous to the last outbreak among Americans, the Guamanian infants and small children practically all had neutralizing antibody to the Lansing strain of virus.[3,29] A very high percentage also had antistreptolysin "O" antibody[3,29] and had negative Schick reactions.[31] Thus, it was apparent that though showing both clinical and direct immunologic evidence of immunity to poliomyelitic, diphtherial and streptococcal infections, the agents of these diseases continued to spread rapidly and

regularly through the population, not hindered seriously by the immune state, as were rubeola and other diseases which disappeared following outbreaks. It would appear, therefore, from this and other supporting evidence which I have summarized elsewhere,[3] that immunity in poliomyelitis, unlike that in rubeola, probably does not permanently or completely prevent reinfection and a temporary carrier state. It will be recalled that the chimpanzees of Howe and Bodian[13] were not prevented from becoming infected by the administration of serum.

One additional source of information on reinfection in poliomyelitis must be mentioned because it appears to challenge the conclusions just drawn. Both Bodian and Howe[32] and Melnick and Horstmann[33] have found that chimpanzees are generally refractory to infection by mouth to the same strain of virus with which they had been recently infected. The duration of this type of immunity is as yet unknown, but, in view of other known facts it could well be temporary, though more durable and more complete than that coming from passive serum protection.

If immune serum does not completely prevent infection, is it not possible that active immunity of a more permanent nature might be acquired during a period of passive protection, at least during its waning phase, if the individual is meanwhile exposed to infection in an epidemic area? We have worked with a common, highly fatal, virus disease of cats, panleucopenia, where this immunologic mechanism appears to work in nature (reviewed in 3). Kittens born of immune mothers become actively immune through exposure and inapparent infection. Veterinarians use this principle of combined serum and the living pathogen in some of their immunization procedures, and two groups of workers[34, 35] have demonstrated that active immunity is engendered in mice infected with the M.M. virus during the period of maternally acquired passive protection. The M.M. virus is a neurotropic agent having some properties similar to those of poliomyelitis. More recently, Stokes[36] has shown that during an outbreak of infectious hepatitis in children, passive protection with gamma globulin apparently led eventually to active immunization, since the protection lasted at least five months during contact with constantly developing disease in the uninoculated controls. The protective effect of gamma globulin could hardly be expected to last five months, yet during this period cases occurred in the uninoculated controls who mingled intimately with the inoculated. No cases developed in the latter. After nine months a sample of the latter were subjected to experimental infection and resisted, while disease developed in a reasonable proportion of a group of controls from another environment.

From this evidence I believe it quite possible that serum prophylaxis administered to children during a poliomyelitis epidemic probably would not entirely prevent poliomyelitis infection and the concomitant development of an active, more durable immunity. Neither would it necessarily arrest or deter spread of the virus in the community by greatly reducing the number of persons susceptible to infection and a carrier state. The infection might be entirely inapparent or lead to mild nonparalytic disease or to some modification of an otherwise more severe outcome. However, these facts must still be demonstrated experimentally!

In the light of the data now available and pending the possible development of a safe, effective and not too costly vaccine for active immunization, a well controlled experiment with gamma globulin would appear to be in order. Gamma globulin from blood of adult Americans would have the advantage of containing antibody to all the immunologic types of virus common in this country.[11] If protection occurs at all it cannot be counted

on for a period of time in excess of six weeks unless infection occurs and converts the protection to an active immunity. One, two or three injections in children up to 10 or 12 years of age during each epidemic season might prove to be a practical means of protection and it is a means which is now available, depending only on the collection of adequate amounts of adult blood for processing.

Active Immunization

Active immunization presents a much more complex problem and, if ever available, is certainly still removed from us by a span of several years at least. Here one is faced with the problem of multiple immunologic types, and the development of methods of inexpensive commercial scale production of virus which is now available only at large cost in minute amounts and with no known method of effecting a change. I state this even while having knowledge of the recent experimental growth of Lansing virus in human foreskin tissue culture,[37] and the growth of two strains of virus (Lansing and Brunhilde) in human embryo tissue culture.[37,38] In addition, there are the dangers of multiple inoculations of brain tissue, the only present source of even moderately large supplies of virus. Furthermore, there is the need of repeated injections for many years, probably annually, for unless safe mutant strains of each type miraculously appear, as have been discovered so far only for yellow fever and smallpox, inactive (killed) virus must be employed. Since time is required to develop antibody following vaccination, thus differing from passive immunization, vaccine administration should anticipate an outbreak by being given annually in the spring and not be reserved for those years when evidence of an outbreak has already appeared.

One objection to vaccination which previously was held—that of preventing naturally acquired immunity and thus directly or indirectly eventually building up a population of all ages fully susceptible unless annually vaccinated—possibly need no longer be held if immunity, as previously discussed, does not entirely preclude natural infection of the individual, and if the presence of a large number of artificially immunized children does not decrease the dissemination rate in the general population. However, the results of the chimpanzee experiments suggest that active immunity is more likely to produce at least temporary resistance to reinfection and a carrier state, than does passive. We have only one carefully controlled experiment in another infection, from which positive information of such an epidemiologic nature is available. These findings may or may not be applicable to poliomyelitis. MacLeod and his co-workers[39] actively immunized half of a large closed population with the capsular polysaccharide of several types of pneumococci. This resulted not only in a reduction of cases in the immunized group but also to a less degree in the nonimmunized, and furthermore, it reduced the carrier rate in the immunized group. They conclude that, "the ability of the immunized subjects to carry and disseminate types I, II, V and VII pneumococci was greatly reduced by specific immunity to these types and that this immune barrier, composed of half the population, greatly reduced the dissemination of these types throughout the whole population." Experience on Guam, nevertheless, under conditions of naturally acquired immunity and transmission existing there, suggests that for diphtherial, streptococcal and poliomyelitic infection, this is no serious barrier to the dissemination of infection. Obviously, it is impossible to interpret adequately either of these observations without further experiment and observation.

One other practical problem does present itself, however, that expressed in the first

quotation read,[1] to the effect that very large numbers who would never become paralyzed would be injected with vaccine to prevent a very few from the rare paralytic manifestation of this ordinarily benign infection. This same criticism might be leveled at passive immunization, but as I will point out, not to quite the same degree. First, however, just what are the facts regarding the annual chances of fatal or crippling infection and what precedent exists for immunizing against a disease so rarely associated with fatality and sequelae?

The average annual experience with poliomyelitis over a recent 20 year period in four Northeastern states (Connecticut, Massachusetts, New Jersey and New York), among our most heavily affected areas, is 37 reported cases per 100,000 children in the 0 to 9 year age groups.* This age group accounts for about two thirds of all cases and presumably vaccination would first be applied in this group. Only about 25% of reported cases in this age group die or end in residual paralysis of any significance, according to most analyses. If vaccination is practised annually and by good fortune should give 100% protection, this means that approximately 11,000 children would have to be immunized annually to prevent the annual average occurrence of each single fatal or permanently disabled child. This estimate is based on experience in the communities and in the age groups where the incidence is considered highest. Inclusion of children of ages above 9 years and extension to Southern states would increase this ratio to well over 1 per 11,000, even to 1 per 50,000 or more in many instances. Is this practical and justifiable?

Are any other diseases with such a low morbidity or mortality rate now included among those for which we vaccinate? Pertussis appears to approach it most nearly. In the United States, just prior to the general use of pertussis vaccine, for an annual 200,000 reported cases only 5,000 deaths occurred, while for 4,000 to 5,000 annual cases of poliomyelitis about 600 deaths occur. Here, the deaths from pertussis equal the total reported cases of poliomyelitis, making the probable excess in deaths or permanent sequelae only two to four fold greater for pertussis. But, 85% of the pertussis deaths occur under 2 years of age and it is to prevent these that the vaccine series is given once in infancy and occasionally a recall dose given one year later. This places pertussis immunization on an entirely different rationale. The immediate risk in the group vaccinated is far greater than in poliomyelitis. Diphtheria immunization is practised not because of present rates, but for the experience observed before it was reduced. The older figures for diphtheria are far in excess of the present and thus in no way comparable to those for poliomyelitis.

It appears, therefore, that vaccination, if performed annually, would represent a far greater effort, expense and risk of accident to thousands to protect a single individual, than for other diseases for which vaccination is employed. However, let us now consider in more detail whether it would be essential to vaccinate annually, or whether, as suggested for gamma globulin, it might be reserved for use in epidemic years only. Primary vaccine immunization would require considerable time and a series of injections of as yet unknown volume and number. This would probably be given arbitrarily in the spring, possibly the second spring of life. A single recall injection would be expected to stimulate immunity more rapidly than the primary series, so it may be questioned

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* Calculations based on data from Tables 1 and 3 from Dauer, C. C., Trends in age distribution of poliomyelitis, Am. J. Hyg. **48**:133, 1948.

whether it would be necessary to give it until after possibly two or three years as in diphtheria, unless an epidemic or known exposure occurred sooner. This point might be argued. One factor to be taken into consideration is the possible deleterious effect for an undetermined number, of giving a large dose of antigen late in the incubation period of the infection, if the recall dose is reserved to be given following exposure during the early phase of a poliomyelitis epidemic. Annual vaccination is now performed for Japanese B. encephalitis in horses and man, for Western equine and Eastern equine encephalomyelitis in horses and in human laboratory workers. These are all inactivated neurotropic virus vaccines. This appears to be the accepted pattern for use of such agents. It is my opinion that recall doses of an inactivated poliomyelitis vaccine should be given annually during the first decade of life, at least. On the other hand, gamma globulin would only be given at times of probable unusual exposure, ordinarily during the early phase of an epidemic. Its effect would be immediate and would represent no danger to any child, even if given late in the incubation period.

It appears, therefore, that of two potential immunizing agents, each of unknown value, there is a good indication for field tests of gamma globulin. Gamma globulin is immediately available for trial and from a theoretic, immunologic standpoint seems to be much more practical to employ than a vaccine. However, I would be very much opposed to the general use of gamma globulin for this purpose, by pediatricians or others, until it has been adequately tested with suitable controls. It is definitely an experimental agent of unproved value.

Specific Therapy and Prophylaxis

Too many recent reviews have been written on the subject of chemotherapy and prophylaxis and of antibiotic therapy and prophylaxis to justify a repetition here.[40–50] It should be adequate to state, for those who have not been following this already bulky and rapidly growing literature, that the developments of recent months and years show this field of research to be well beyond the diaper stage. Numerous agents have now been shown to be active against the larger viruses and several have shown definite inhibition of some of the smaller ones. As in all rapidly developing fields false claims appear and the reader must separate the chaff from the grain. So far, no report of a reliable nature has appeared for a practical therapeutic or prophylactic agent for poliomyelitis, but it would be no surprise if such a report were written within the next months or the next year, though I assure you I have no "inside" information of such an impending announcement. So many "miracle" drugs have been found in recent years which have relieved the need of more costly or unavailable preventive measures that we can at least hope that this will soon be the case for poliomyelitis. Then, we can concentrate on the rapid cure of a relatively small number of cases and forget about the thousands who escape without diagnosable disease.

Summary

Particular emphasis is placed on possibilities of passive immunization, because it is felt that this offers practical and theoretic advantages over active immunization. A vaccine is not available at present and may never be available in adequate quantities for all immunologic types or at reasonable cost. Furthermore, if an inactivated vaccine is used, annual revaccination for duration of life might logically ensue. Experimental work has demonstrated the effectiveness of serum prophylaxis in animals and has been given

field trials in man, the results of which are suggestive but inconclusive. Gamma globulin from adults should contain antibody to all prevalent types and has been shown to be active in monkeys against three types. It has been used on a small scale as a human prophylactic agent but not on an experimental basis. Gamma globulin, on the basis of inadequate experiment and epidemiologic reasoning, might not prevent infection, though it would be expected to prevent clinical disease. If this proves to be a fact, it would not prevent the development of permanent immunity through inapparent infection, a decided practical advantage. Its use would be recommended only during epidemic years and for only the more susceptible age groups. Dosage and interval would have to be determined. Since gamma globulin is now available, it is felt that a carefully controlled field experiment to determine its effectiveness is in order. There is still no evidence that a serum, gamma globulin or other immunologic agent, has any therapeutic effect, or abortive effect, once illness has begun.

So far, no report of a reliable nature has appeared for a practical therapeutic or prophylactic antibiotic or chemotherapeutic agent against poliomyelitis. However, developments in this field as applied to rickettsial diseases and a few other virus diseases lead to considerable optimism. It is believed that the most likely final control methods will be developed along these lines.

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SPANISH ABSTRACT

La Posibilidad de una Prevencion Especifica en el Tratamiento de la Poliomielitis

El autor destaca la posibilidad de una inmunización pasiva en el tratamiento de la poliomielitis y las ventajas practicas y teoreticas de ésta, sobre la inmunizacion activa. Actualmente no existe una vacuna, y quizás una nunca sea desarrollada, la cual comprenda todos los tipos inmunologicos de la enfermedad y pueda ser producida en cantidades adecuadas y a costo razonable. Además, si una vacuna inactivada fuera usada, logicamente seria necesario la revacunacion anual. En relacion con la inmunizacion pasiva, trabajos experimentales han demonstrado la eficacia de sueros profilacticos usados en animales, pero los resultados en humanos aunque sugestivos aun no son definitivos. Se estima que la gamma globulina del suero de adultos debe contener anticuerpos contra todos los tipos de poliomielitis prevalente y su uso eficaz ha sido demonstrado en monos infectados con tres tipos diferentes de virus poliomielitico. La gamma globulina ha sido usada en pequeña escala como un agente profilactico en casos humanos, pero no desde el punto de vista experimental. Basándose en una evidencia experimental inadecuada y un razonamiento epidemiologico, puede esperarse qu las gamma globulina puedan prevenir el desarrollo clinico de la enfermedad aunque no prevenga la infeccion. Si esto último llegara a ser un hecho comprobado, tendria una ventaja practica decisiva, ya que la infeccion inaparente no evitaria el desarrollo de inmunidad permanente. El uso de las gamma globulinas seria recomendado durante los años de epidemias y solamente usada en el grupo de niños de edad susceptible. La dosis y el intervalo de administración tendria que determinarse. Asimismo, y ya que la gamma globulina está actualmente al alcanze del medico, se sugiere el estudio cuidadoso y controlado de los casos a fin de determinar su eficacia. Por el momento, no hay evidencia que sueros, gammas globulinas u otros agentes inmunologicos tengan efectos terapeuticos o abortivos después del comienzo de la enfermedad. Tampoco existen reportes fiables que demuestren la eficacia terapeutica o profilactica de los antibioticos u otros agentes quimicos en la poliomielitis. Sin embargo, los nuevos descubrimientos terapeuticos de aplicacion practica en las enfermedades causadas por ricketsias y otras enfermedades a virus dan optimismo y sé estima que los metodos finales de control de la poliomielitis se desarrollaran de acuerdo con estas ideas terapeuticas.

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ERYTHROBLASTOSIS FETALIS

IV. Further Observations on Kernicterus

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PREVIOUS studies[1] reported by the present authors have indicated that it is not possible in reviewing a large series of cases of erythroblastosis fetalis seen between 1937 and 1948 to show an improvement in over-all mortality in relation to any specific method of treatment, except so far as death due to uncomplicated anemia may be avoided by blood transfusion in most babies who survive the first day of life. It has been shown,[2] on the other hand, that the outcome of erythroblastosis fetalis in the Rh-positive fetus of a sensitized Rh-negative mother is closely related to maternal reproductive history, maternal titer of anti-Rh substance, and length of fetal gestation. In live born infants the chances of recovery were shown[3] to be inversely related to the degree of anemia and hepatosplenomegaly at birth, but kernicterus, which is the most frequent concomitant of an unfavorable outcome in live born infants with erythroblastosis fetalis, appeared unrelated to these other signs of disease.

It is proposed to review kernicterus from clinical and pathologic standpoints, and to indicate possible directions of study which might lead to its prevention. Those elements which have previously been shown to have a relation to the outcome in general of erythroblastosis fetalis will be reviewed for their specific effect on the incidence of kernicterus in live born infants. The group of infants studied includes all live born infants with erythroblastosis fetalis born at the Boston Lying-in Hospital from 1945-1948, or admitted to the Children's Hospital, Boston, in 1947-1948.

FREQUENCY OF KERNICTERUS

The importance of kernicterus as a complication of erythroblastosis fetalis is of relatively recent recognition. In 1941 Sanford[4] was able to find only 26 reported cases of kernicterus in medical literature, only six of which were thought to be associated with erythroblastosis fetalis. The same author[5] has since that time recorded the rarity of kernicterus, even among erythroblastotic babies. The first studies emphasizing the frequency of kernicterus, among which were those of Docter[6] and Vaughan,[7] did not appear until some years after the discovery of the relationship of erythoblastosis fetalis to maternal sensitization to the Rh factor, and the incidence of kernicterus has since been reported as high as 55%[8] of live born infants with erythroblastosis.

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The frequency of kernicterus in the group of live born infants studied by the present authors has been 12% (table 1). As was indicated before,[1] this percentage may be somewhat higher than would be encountered in a group of infants among whom labor had not been induced in the sensitized mother. Among such babies the incidence of kernicterus might be less than 10%. It is thus assumed that this clinical material may be different from that seen in other clinics, especially those clinics where early induction of labor in the sensitized woman has not been practiced.

TABLE 1

INCIDENCE OF KERNICTERUS

(Boston Lying-in Hospital, 1945–1948, Children's Hospital, 1947–1948)

Total live born infants with erythroblastosis	224	
Total kernicterus (% of total)	26	(11.6%)
Total surviving infants	184	
Kernicterus, surviving (% of total surviving)	9	(4.9%)

Approximately one third of the patients with kernicterus seen during this period have survived the first week of life (table 1). They constitute 5% of all surviving infants seen during this time. Each of the surviving infants with kernicterus shows some neurologic disorder, ranging from mild motor incoordination with essentially normal intellectual function to extremely severe motor disability with idiocy.

CLINICAL MANIFESTATIONS

The signs of kernicterus in an infant with erythroblastosis fetalis are sufficiently characteristic that the diagnosis can be made or excluded with confidence during the first week of life. In babies with acute erythroblastosis fetalis, the deaths which occur after the first and before the sixth day of life will usually be associated with kernicterus. The usual antemortem clinical course of such infants can be characterized as follows:

The Rh-positive infant of a sensitized Rh-negative mother develops jaundice during the first day of life. There may or may not have been clinical signs of erythroblastosis fetalis at birth, but the condition of the infant is generally not alarming on the first day, and neurologic examination discloses nothing abnormal. The jaundice usually becomes marked in intensity by the second or third day. Some time after the first day of life, the baby becomes lethargic and feeds poorly. Refusal of food and regurgitation or vomiting frequently occur. The baby is likely to respond feebly to stimulation.

The nearly pathognomonic signs of kernicterus which may then become manifest are disappearance of the normal Moro response and the appearance of a tendency to spasms of opisthotonos, in which the arms are rigidly extended and inwardly rotated, and the fists clenched. This pattern becomes the obligatory response of the infant to a startling stimulus, such as would normally call forth the Moro reflex. This pattern may occur also as spontaneous periodic spasms of opisthotonos and rigidity, often accompanied by a sharp, high-pitched cry, which subsides in a few seconds, as the baby lapses into lethargy and relative atonia. Convulsions in kernicterus are rare in the authors' experience, except terminally. Jitteriness, or tremors, or hyperreflexia in babies with erythroblastosis fetalis are not suggestive of kernicterus. Occasionally a tendency to head retraction will be associated with hunger or position of comfort in babies who are otherwise alert and active, and

whose Moro responses are normal, under which circumstances it need not be regarded with alarm. There seems to be no other single neurologic sign of such reliability as opisthotonos in the diagnosis of kernicterus, but the interpretation of mild tendencies to retraction of the head on stimulation should always integrate with it other aspects of the infant's behavior, such as feeding activity, general alertness, and presence or absence of a normal Moro response.

Death in acute kernicterus is ordinarily preceded by a period during which the baby's respirations become irregular, gasping and infrequent. The baby's color becomes poor, rales are heard in the chest, and a bloody discharge often appears in the upper respiratory tract. A loud cardiac murmur may be heard which was not heard previously. Death follows within a few hours, and is apparently due to respiratory failure. The clinical signs are those of pulmonary hemorrhages.

Babies with erythroblastosis fetalis who die during the first five days usually have clinical evidence of pulmonary hemorrhage as manifested by bloody discharge from the nose and mouth and rales in the lungs. In the authors' series babies with kernicterus who have died during the first five days have almost invariably had these signs of pulmonary hemorrhage, which is ordinarily evident pathologically as microscopic alveolar hemorrhage. The relation of pulmonary hemorrhages to kernicterus is not clear. It has been suggested[7] that they are associated with various types of intracranial lesions in the newborn period, of which kernicterus is only a specific instance. In babies with erythroblastosis fetalis who die of pulmonary hemorrhages without kernicterus, the hemorrhage may be secondary to brain injury from anoxia due to anemia, atelectasis or both, or may be the result of a more fundamental process, possibly toxic.

Infants with erythroblastosis fetalis who survive the first five days of life without any signs of kernicterus (of which the most subtle is a constant tendency to mild opisthotonos when the startle pattern is elicited), will usually make a complete recovery, so long as proper attention is given to the possible development of anemia.

Any babies with neurologic signs of kernicterus who do not develop the clinical signs of pulmonary hemorrhages within the first five days of life are likely to survive the acute phase of erythroblastosis fetalis. They will nearly always show an extrapyramidal motor defect in later life, usually with mental retardation. The severity of residual signs in six closely followed infants in this series is graded as follows: severe, 3 cases; moderate, 1 case; mild, 2 cases. The outlook for ultimately adequate function in the two mildly affected children appears excellent.

Pathology of Kernicterus

The definitive sign of kernicterus seen at post mortem when death occurs during the acute phase is the golden yellow pigmentation of the nuclear masses of the brain, seen in gross, which gives the disease its name. This pigmentation is most characteristically found in the basal ganglia, the hippocampal area, the dentate nucleus of the cerebellum, the inferior olive, and in the vegetative centers of the medulla. Pigmentation of the surface of the brain is commonly seen only in the mammillary bodies and in the cerebellar flocculi. The hippocampal gyrus may also be seen to be discolored.

Microscopic abnormalities in the brains of babies with kernicterus in this series were often absent, even when the gross pigmentation was severe. This is in agreement with the experience of others.[7] In table 2 the degree of microscopic pathologic change seen in the brains of infants with kernicterus examined at the Children's Hospital from 1945-

1948, is related to the duration of life.* When death occurred within the first 72 hours of life, a fair proportion of the brains examined showed no changes or nonspecific changes, not diagnostic of kernicterus, whereas when the duration of life was longer than 72 hours, the pyknosis and pigmentation of cells which were considered to be characteristic of kernicterus were uniformly found. When an infant with kernicterus survives the acute period of the illness for an extended period, the brain will ordinarily show disappearance of neurones and proliferation of glia in those areas where the pigment is seen in the acute phase.

TABLE 2

RELATION OF AGE AT DEATH TO HISTOLOGIC FINDINGS IN KERNICTERUS
(17 Autopsied Cases, Children's Hospital, 1945–1948)

Histologic findings	Age at Death	
	Less than 72 hr.	72 hr. or more
Absent or slight	7	0
Moderate or severe	4	6

The location of the gross and microscopic abnormalities in kernicterus is generally consistent with the clinical manifestations of the disease. Those infants who survive with a defect closely confined to the motor system would appear to have had involvement only of the basal ganglia, the most characteristically pigmented area. In those infants who die of kernicterus with pulmonary hemorrhages it may be the involvement of the medullary centers which leads to disturbed respiratory dynamics and vascular collapse. That brain injury in kernicterus may not necessarily be confined to the areas where pigment is found is suggested by the widespread loss of cortical function in some surviving infants.

It is not known whether the pigmentation of brain cells is primary or secondary to their injury, nor whether, in fact, pigmentation of cells will always be seen in the brains of babies with erythroblastosis fetalis who die of that functional disturbance which we generally recognize clinically and pathologically as kernicterus. The authors have seen one or two instances of infants dying after the first day of life of acute erythroblastosis fetalis with pulmonary hemorrhages where the antemortem course was indistinguishable from kernicterus, but that lesion was not found at necropsy.

No changes have been found in other organs of the body which may be considered necessarily to accompany kernicterus. The changes characteristic of the hemolytic process in erythroblastosis fetalis, such as enlargement of the liver and spleen, cardiac hypertrophy, and extramedullary erythropoiesis, may or may not be present. The liver may show conditions varying from normal to extensive acute necrosis of liver substance. Whether parenchymal changes in the liver have any relationship to kernicterus is not known, but it seems apparent that simple hepatic extramedullary erythropoiesis has none.

ANTENATAL CONSIDERATIONS IN KERNICTERUS

It has been shown before[2] that while the over-all prognosis of erythroblastosis fetalis is related both to maternal history and to maternal titer of antibody, the outcome for

* The authors are indebted to Dr. Benjamin H. Landing, of the Department of Pathology, Children's Medical Center, for the examination of the microscopic sections.

live born infants is more closely related to maternal titer than to past history of an affected infant. The data given in table 3, however, indicate that if there is a past history of a previous affected infant with kernicterus, then there is a substantial increase in the chances that a subsequent live born Rh-positive infant will also have this complication of erythroblastosis fetalis. It is striking, on the other hand, that if there is a history of previous erythroblastotic infants none of whom developed kernicterus, then kernicterus

TABLE 3

RELATION OF PAST HISTORY TO INCIDENCE OF KERNICTERUS
(Boston Lying-in Hospital, 1945–1948, Children's Hospital, 1947–1948)

	Maternal History					
	No previous erythroblastosis fetalis or transfusion		Erythroblastosis fetalis or transfusion; no kernicterus		Previous baby with kernicterus	
	No.	%	No.	%	No.	%
Kernicterus	14	11	4	5.4	8	38
Recovered	105		58		12	
Died, no kernicterus	10		12		1	
Total	129		74		21	
			$\chi^2=13$		p. = <.01*	

* Columns 2 and 3 were compared in the calculation of χ^2, lines 2 and 3 were combined.

in a subsequent live born baby with erythroblastosis fetalis is no more likely than if there had been no previous affected infant at all. The chances are very small that these figures do not indicate a familial tendency to kernicterus. This might depend upon susceptibility of the infant which is genetically determined, or upon some particular aspect of the individual mother's response to sensitization or to incompatible pregnancy which tends to repeat itself in successive pregnancies.

Table 4 shows the relationship of outcome of erythroblastosis fetalis in live born infants to maternal titer, and shows that the chief hazard of high titer is an increased likelihood of kernicterus, rather than of death due to other causes. It has been shown that a titer of 1:64, such as is displayed by 80 mothers in table 4, carries a high risk of stillbirth, and it can be estimated that for these 80 mothers with high titer who gave birth to living infants, there were another 63 mothers with high titer who delivered stillborn infants. It is surprising that the high maternal titer, which leads to such a high incidence of stillbirths and of kernicterus, does not lead to an increased incidence of that severe illness in live born infants which leads to early death and is not associated with kernicterus.

Table 5 summarizes the relationship of outcome of erythroblastosis fetalis to length of fetal gestation, and indicates clearly that in this series of patients delivery at less than 38 weeks' gestation was associated with increased numbers of babies with kernicterus as well as increased numbers of deaths in the newborn period without kernicterus. Detailed treatment of these figures elsewhere[1,2] has shown that, while the number of infants born before 38 weeks' gestation has been increased by early induction of labor in sensitized women, it is more likely immaturity which is responsible for the increase in kernicterus

TABLE 4

RELATION OF MATERNAL TITER TO OUTCOME IN LIVE BORN INFANTS
(Boston Lying-in Hospital, 1945–1948, Children's Hospital, 1947–1948)

	Highest Prepartum Maternal Titer*					
	Less than 1:64		1:64 or more		Unknown	
	No.	%	No.	%	No.	%
Recovered	99	84.5	58	72.5	18	66.5
Died, no kernicterus	11	9.5	8	10.0	4	15.0
Kernicterus	7	6.0	14	17.5	5	18.5
Totals	117		80		27	
Still births (estimated total from Boston Lying-in Hospital data alone)	10		63		8	
			$\chi^2=5.5$, $p<0.05$†			

* Highest titer in bovine albumin.
† Columns 1 and 2 compared in calculation of χ^2, lines 1 and 2 combined.

TABLE 5

RELATION OF LENGTH OF GESTATION TO OUTCOME IN LIVE BORN INFANTS
(Boston Lying-in Hospital, 1945–1948, Children's Hospital, 1947–1948)*

	Period of Gestation			
	38 wk. or more		Less than 38 wk.	
	No.	%	No.	%
Recovered	131	89	43	58
Died, no kernicterus	8	5.5	14	19
Kernicterus	8	5.5	17	23
Totals	147		74	
			$\chi^2=11.4$, $p<0.01$†	

* Gestation unknown in 3 Children's Hospital cases.
† Lines 1 and 2 combined in calculation of χ^2.

than the possibility that those mothers were selected for induction whose babies had an inherently bad prognosis. This increased risk due to immaturity has to a considerable extent nullified the gains made through induction of labor in the prevention of stillbirths.

PARANATAL CONSIDERATIONS IN KERNICTERUS

The probability of the occurrence of kernicterus in erythroblastosis fetalis can be roughly estimated before birth on the basis of the various considerations just discussed. There is very little that can be added to the evaluation of the infant's prospects by clinical or clinicopathologic examination at the time of birth.

The previously reported data[3] indicated that while the over-all prognosis for recovery

from erythroblastosis fetalis bore a close relationship to the degree of anemia and hepatosplenomegaly present at birth, the occurrence of kernicterus was not closely related to these signs, and seemed to complicate about 12% of cases in any category of clinical severity of disease. The data on the time of onset, intensity and duration of jaundice were not felt to be complete or objective enough for statistical analysis, though mild or early clearing icterus had been considered a favorable sign. Data accumulated since the time of this previous report have brought into sharp prominence the fact that kernicterus occurs almost exclusively in those infants in whom jaundice is marked.

Serologic studies in the infant have been of little help in this series of cases. The Coombs test has not proved an accurate index of the severity of illness in these babies, and in at least two cases of kernicterus has been repeatedly negative. Serum levels of antibody in the infants have shown no correlation with outcome, except that in the offspring of mothers who have a high titer, the infant's low titer or absence of free serum antibody is probably an unfavorable prognostic sign.[3]

Kernicterus has been about twice as common in this series of cases in male (16%) as in female infants (6%). This result is statistically significant ($p < .05$).

Discussion

From a clinical standpoint it is difficult to escape the conclusion that kernicterus is a disease of neonatal life, not necessarily dependent upon functional or structural changes in the brain which might have occurred before birth, since most babies who develop signs of kernicterus appear to be in good condition at birth, and give normal neurologic reactions for a definite period of time before the signs of kernicterus appear. The authors have not encountered a pathologic lesion indicative of kernicterus in a stillborn fetus, nor in a live born infant who lived less than 38 hours. Moreover, the early delivery of an infant with erythroblastosis fetalis carries with it a substantial increase in the likelihood of kernicterus which surely indicates that this complication is not the result of cumulative injury dependent upon length of intrauterine exposure to maternal antibodies.

Additional presumptive evidence of the postnatal nature of kernicterus is given by the histopathologic findings which indicate that in an infant with developing kernicterus a certain minimum duration of life after the onset of brain injury may be necessary for the characteristic microscopic changes to appear. That essentially normal brains from a microscopic standpoint are found in any appreciable number of these infants is strong evidence that the train of events leading to death with kernicterus is initiated not more than a few hours before death may ensue.

While it is generally conceded[9] that death in erythroblastosis fetalis is rarely due to anemia alone, Mollison[10] has presented evidence which he feels relates the likelihood of kernicterus to the intensity of the hemolytic process at birth. He suggested that it is the tendency of those infants most severely anemic at birth to die so soon that kernicterus has no chance to appear which has led Parsons[11] and Vaughan,[7] among others, to suspect an inverse relationship between degree of anemia and likelihood of kernicterus. The present investigators' previously reported data[3] dealing with the relationship of kernicterus to the severity of anemia at birth do not seem to support this view, since kernicterus occurred in about 12% of cases of erythroblastosis fetalis placed in any category of clinical severity with respect to degrees of anemia and hepatosplenomegaly at birth. Of the babies whom the authors placed in the category of most severely affected, as many as 50% recovered,

while certain infants with little or no signs of illness at birth suffered kernicterus without anemia presenting a therapeutic problem at all.

The authors' more recent data, from a larger series of cases, indicate a tendency for kernicterus to occur with greater frequency in babies more seriously ill at birth, as Mollison found. There is strong reason for believing that this may depend in large part upon the fact that such babies may have a higher level of serum bilirubin in the course of their illness than babies mildly or not affected at birth, and it is believed that in the latter group of infants a high level of serum bilirubin may play an important role where kernicterus occurs.

There no longer seems to be any reason to postulate an inverse relationship between the likelihood of kernicterus and the degree of blood disease in erythroblastosis fetalis. It is true, as indicated in a previous study,[7] that in an unselected group of live born infants the number of babies with mild or no anemia at birth who develop kernicterus will exceed the number of babies with severe anemia who develop that complication, and that the number of mildly affected babies who develop kernicterus may be exceeded by the number of babies very ill at birth who make a satisfactory recovery. But the proportion of babies with kernicterus may vary little between any two groups of infants, and the above effects will likely be due simply to the fact that in an unselected series of cases mildly affected infants will be numerically predominant.

The notion is not new that kernicterus may depend upon some important pathologic process in certain infants with erythroblastosis fetalis which is different from that process which leads to anemia and hepatosplenomegaly. The hypothesis gains support from the observations of Yannet and Lieberman,[12] who found that brain damage associated with incompatibility in the ABO system of blood antigens may often not be associated with any clinically recognized hemolytic anemia at all. Their data do not indicate that the brain damage with ABO incompatibility is due to the same mechanism which leads to kernicterus in Rh incompatibility, but the possibility is clearly given weight that in both conditions brain injury may not depend necessarily upon a hemolytic anemia arising out of demonstrated blood group incompatibility. On the other hand, the authors have seen typical cases of kernicterus in cases of ABO incompatibility where attention was drawn to the illness only because the presence of anemia with jaundice had raised the possibility that erythroblastosis fetalis due to Rh incompatibility might be present.

Since the authors' recent data indicate that kernicterus in erythroblastosis fetalis may depend at least in part upon the presence of an elevated serum bilirubin, it must clearly be inferred that the hemolytic process may contribute to the occurrence of kernicterus insofar as it leads to jaundice. On the other hand, since kernicterus may occur in the presence of jaundice which does not depend upon a hemolytic anemia, and since many deeply jaundiced babies with erythroblastosis fetalis do not develop kernicterus, it is of interest to speculate upon the possible nature of a fundamental disturbance or condition in the brain which renders some infants susceptible to kernicterus when the serum bilirubin is elevated, and in the absence of which other infants find an elevated serum bilirubin tolerable.

The search for a pathologic process unique in those babies with erythroblastosis fetalis who develop kernicterus has followed two main currents of thought: first, that kernicterus may depend upon direct injury of fetal cerebral or other tissue by maternal antibody,[7] and second, that kernicterus is consequent upon or associated with liver injury,[11] with

analogies seen in hepatolenticular degeneration, certain vitamin deficiencies and other diseases. There is no evidence that kernicterus depends upon plugging of cerebral vessels by cellular agglutinates such as Wiener[13] has reported having seen.

The finding that, in the Rh-positive offspring of mothers with high (hyperimmune) titers, a very low titer in fetal serum carries a worse prognosis than high titers, recalls Vaughan's suggestion[7] that the affinity of antibody for fetal tissue may be related to the severity of erythroblastosis fetalis. However, the data at hand indicate that the likelihoods both of kernicterus and of acute deaths without kernicterus are increased when the maternal-fetal titer ratio is high. It is not possible therefore to distinguish kernicterus from other forms of severe erythroblastosis fetalis with respect to this evidence of increased tissue-antibody affinity.

The time of onset of the hemolytic anemia, possibly the time of onset of the processes leading to kernicterus, and very possibly the maternal-fetal titer ratio may depend on such a fetal serum component as Witebsky[14] has described, which supports the agglutination of Rh-positive red blood cells coated with hyperimmune antibody, and the appearance of which in fetal serum is dependent upon increasing maturity in the late prenatal and early postnatal periods. It is difficult to postulate a relationship of kernicterus, however, to a process dependent upon increasing fetal or neonatal maturity, since premature delivery does not decrease, but increases, the likelihood of kernicterus, and since kernicterus is seen only within a relatively restricted period of neonatal life, regardless of the length of fetal gestation.

Wiener[15] and Vaughan[7] have suggested that antibody transfer to the infant during labor might be responsible for the occurrence of kernicterus, but it is extremely unlikely that such transfer accounts, if it occurs at all, for any observed clinical phenomena. The fetal serum antibody titer in Rh-negative infants of sensitized mothers is virtually the same as the maternal (hyperimmune) titer in every case, indicating that maternal and fetal antibody are likely in as close equilibrium for long periods before delivery as the rate of absorption of passively transferred antibody by fetal tissues permits. Any increment in fetal antibody content which was dependent on labor would likely be trivial. Moreover, the fetal titer is decreased, in general, rather than increased in the infants with worst prognosis. Certain Rh-positive infants may carry for weeks without harm high titers of serum antibody.

In short, while kernicterus may depend upon a specific injury to certain fetal tissues by maternal antibody, the available data on relationship of fetal serum components to course and outcome of erythroblastosis fetalis give no useful information bearing on this contention.

There are enough instances of associated metabolic disorders of the liver and nervous system to have brought the attention of a number of workers to the possibility that kernicterus may be related to liver injury, but there has been as yet no definite characterization of such a relationship. Fairly extensive liver function studies in acute erythroblastosis fetalis have, in the authors' series, generally indicated normal function except for the increased retention of bromsulphalein dye usually seen in newborn infants,[16,17] and except for hyperbilirubinemia. It is not clear to what extent in various infants this last sign is an index of hemolytic process or of hepatic insufficiency. The authors' impression is that in babies with kernicterus jaundice is generally marked, and that when these babies survive, the jaundice is prolonged. The jaundice of a baby with kernicterus often

seems disproportionate to the degree of anemia, and a number of instances have been seen of untreated babies surviving with kernicterus where anemia did not present a significant therapeutic problem at any time in the course of the illness. Under these circumstances jaundice can much better be explained on the basis of excretory insufficiency of the liver than as a result of blood destruction.

Various substances designed to support liver function have been used or recommended in erythroblastosis fetalis, including crude liver extract,[18] choline,[19] methionine,[20] inositol[18] and glucose infusions.[21] Convincing evidence of their efficacy is lacking. A more specific nutrient element, therapeutic in hepatocerebral disease, may in the future prove a uniformly effective prophylactic agent in kernicterus.

It seems clear that an effective therapeutic measure in kernicterus would need to be instituted very early in neonatal life, if not prenatally. The shortening of the gestatory period by early induction of labor clearly has no place in instances where kernicterus is likely to be seen. While prompt exchange transfusion of the infant at birth has not prevented kernicterus, more vigorous replacement therapy, such as Wiener[22] has suggested, may be more successful. This remains to be shown.* It is certain that the proper evaluation of any measure will require extensive trial in a rigidly controlled series of cases. The experiences herein reported invite particular caution against the assumption, in setting up "controlled" series, that any single clinical, hematologic or serologic datum obtained at birth gives an accurate index of the severity of erythroblastosis fetalis, so far as the likelihood of kernicterus is concerned.

Summary

The clinical syndrome of kernicterus in erythroblastosis fetalis is reviewed.

Data are presented which indicate that there is a tendency for the familial occurrence of kernicterus in siblings. Kernicterus is shown to be directly related to the intensity of maternal sensitization, and to the degree of immaturity of the infant. It is more common in male infants than in female.

Evidence is presented that the occurrence of kernicterus in a baby with erythroblastosis fetalis cannot be accurately predicted on the basis of degree of clinical illness at birth, nor on the basis of laboratory examination of the baby's blood at birth.

The possible relationship of kernicterus to hyperbilirubinemia and to other predisposing factors in erythroblastosis fetalis is discussed.

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* In 116 consecutive erythroblastotic infants treated by exchange transfusion between April 1, 1949 and March 1, 1950, only one instance of kernicterus has been seen. This represents a significant reduction in the incidence of kernicterus, but the factor or factors of real importance in relation to this improvement in results are difficult to determine.

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SPANISH ABSTRACT

Eritroblastosis Fetalis

IV. Observaciones Ulteriores en Kernicterus

Los autores revisan el sindrome clinico de la eritroblastosis fetalis. Se presenta data indicando que hay una tendencia familiar en la ocurrencia de Kernicterus en hermanos. Esta complicación está directamente relacionada con la intensidad de la iso-inmunizacion materna y el grado de inmadurez del niño. El kernicterus ocurre mas frecuentemente en varones que en hembras.

Se indica que la ocurrencia del Kernicterus en un niño con eritroblastosis fetalis, no puede predecirse con certeza basándose en el grado de severidad clinica de la enfermedad al nacer, ni tampoco basado en los resultados de los exámenes de sangre del niño al nacer.

La posible relacion del kernicterus con la hiperbilirubinemia y otros factores predisponentes en la eritroblastosis fetalis son discutidos.

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BLOOD CARBONIC ANHYDRASE ACTIVITY IN NEWBORN INFANTS AND THEIR MOTHERS

By MARK D. ALTSCHULE, M.D., AND CLEMENT A. SMITH, M.D.
with the technical assistance of Marion Taylor
Boston

EARLIER workers describe a markedly low level of blood carbonic anhydrase activity in the blood of newborn infants[1-3] and other newborn mammals.[4,5] Since the methods used by these observers exaggerated greatly the differences between the bloods showing high and low activities,[6] it was considered of interest to re-study this matter, using a method which avoids this error;[7] a few observations also have been made on the anemia of pregnancy.

MATERIAL AND METHODS

Fourteen infants were studied. One was 2 wk.' postmature by expected date of confinement, and 3 were premature. The sex and age of each were as shown in table 1. Two infants with erythroblastosis were studied before, during or after exchange transfusion. Observations were also made on the bloods of 6 mothers. The methods used were those described previously.[7,8]

OBSERVATIONS

Hematocrits of the infants' bloods ranged between 27 and 63 per cent cells, with corresponding levels of hemoglobin and numbers of erythrocytes (table 1, chart 1). The

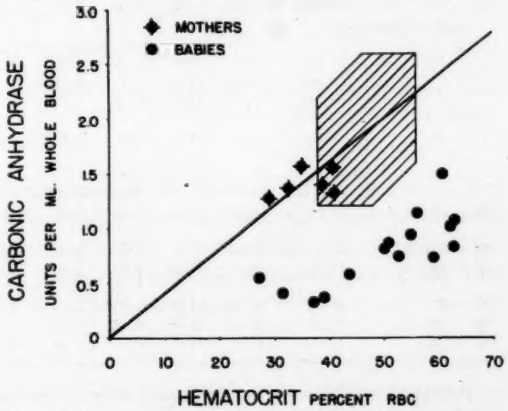

CHART 1. Relation between blood carbonic anhydrase activity and hematocrit. Cross-hatched area is normal adult range; diagonal is drawn from origin to average normal value.

carbonic anhydrase activity of blood obtained at or soon after birth or, in the premature infants, at ages of 21 to 41 days, ranged between 0.3 and 1.5 u./ml. whole blood (chart 1), or 0.9 and 2.5 u./ml. erythrocytes (chart 2). The average was 1.55 u./ml. erythrocytes.

From the Medical Research Laboratories, Beth Israel Hospital, and Laboratory for Research on the Newborn, Boston Lying-in Hospital, and the Departments of Medicine and Pediatrics, Harvard Medical School, Boston.

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TABLE 1

	Initial	Sex	Age	Hematocrit % cells	Hgb. gm.	RBC millions	Carbonic per ml. whole blood	Anhydrase per ml. RBC Units	Birth wt. gm.	Remarks
						Full Term Infants				
1.	A	M	Birth	43.5	13.8	4.12	0.58	1.3	3175	3 hr. labor, normal infant, low forceps.
2.	No	M	Birth	59.0	18.1	5.90	0.74	1.3	4930	2½ hr. labor, normal infant, normal delivery.
3.	H	F	Birth	63.0	19.2	6.14	0.82	1.3	3500	12 hr. labor, normal infant, low forceps.
4.	F	M	Birth	55.0	18.2	5.51	0.94	1.7	4564	7 hr. labor, normal infant, normal delivery.
5.	Bu	F	Birth	52.5	15.9	5.09	0.74	1.4	2860	6 hr. labor, normal small infant, low forceps.
			3 days	50.5	17.1	5.08	0.84	1.7	2860	Wt. 2640. Normal course.
6.	Bo	F	Birth	62.0	18.1	6.11	1.00	1.6	2860	6 hr. labor, low forceps, fetal distress.
			8 days	63.0	20.2	6.01	1.08	1.7	2860	Wt. 2410. Normal course.
7.	P	F	3 days	50.0	18.5	4.99	0.90	1.8	3230	7 hr. labor. Normal infant and delivery, wt. 3090 3rd day.
8.	M	M	4 days	56.0	19.1	5.56	1.12	2.0	3714	Normal infant, mild toxemia in mother, wt. 3120 4th day.
9.	McC	M	6 days	61.0	19.6	5.67	1.50	2.5	3910	Postmature by 2 wk. Otherwise normal—wt. 3260 6th day.
						Premature Infants				
10.	C	M	21 days	39.5	13.3	4.07	0.36	0.9	2013	Mother diabetic and toxemic. Infant normal aside from prematurity. Wt. at 21 days 1930 gm.
11.	Di	M	23 days	31.5	11.5	3.69	0.40	1.3	1820	Mother toxemic. 35 wk. gestation. Infant normal. Wt. at 23 days 2130 gm.
12.	S	F	41 days	27.0	9.9	3.01	0.52	1.9	1417	32 wk. gestation. Wt. at 41 days 2325 gm.
						Erythroblastotic Infants				
13.	Na	F	35 min.	37.0	8.9	2.08	0.32	0.9	3170	Mild hydrops. 38 wk. gestation
			50 min.	40.0	11.2	3.03	0.72	1.8		After 140 ml. out, 125 ml. in.
			100 min.	41.5	12.0	3.88	1.12	2.7		After 410 ml. out, 400 ml. in. (Inf. died 6 hr. later)
14.	Dy	F	1 day	37.0	13.1	4.12	1.40	3.8	2720	After replacement; 445 ml. out, 465 ml. in.
						Mothers at Delivery				
1M.	A		27 yr.	29.0	9.8	3.08	1.28	4.5		Para 1, Gravida 1; resp'y infec., anemia.
2M.	No		35 yr.	41.0	14.1	4.69	1.30	3.2		Para 5, Gravida 5; obesity.
3M.	H		21 yr.	39.0	13.6	4.43	1.40	3.6		Para 2, Gravida 2; Rh.-; no antibodies.
4M.	F		30 yr.	35.0	10.5	4.38	1.56	4.6		Para 2, Gravida 2.
5M.	Bu		27 yr.	32.5	12.4	4.43	1.36	3.9		Para 2, Gravida 2.
6M.	Bo		23 yr.	41.0	13.4	4.47	1.54	3.7		Para 1, Gravida 1.

It is of some interest that the repeat samples on Infants 5 and 6 showed small increases in carbonic anhydrase at 3 and 8 days after birth, while those of Infants 7 and 8 were relatively high at 3 and 4 days. The carbonic anhydrase activity of Infant 9, who was 2 weeks' postmature, was above that of any other infant. On the other hand, 2 of the 3 premature infants presented relatively low carbonic anhydrase activity at about 3 weeks of age. That of the third, Infant 12, was similar to the findings in full term infants during the first week though the baby was almost 6 weeks of age at the time of sampling. The blood of one infant of 38 weeks' gestation with erythroblastosis was similar in carbonic anhydrase activity to that of the premature infants; after exchange transfusion the bloods of this infant and of one other showed, respectively, 1.1 and 1.4 u. of carbonic anhydrase activity/ml. whole blood, or 2.7 and 3.8 u./ml. erythrocytes (chart 2).

The mothers' bloods showed hematocrit values of 29 to 41 per cent cells, with corresponding levels of hemoglobin and numbers of erythrocytes (table 1, chart 1). The carbonic anhydrase activity blood ranged between 1.3 and 1.4 u./ml. whole blood (chart 1) or 3.2 and 4.6 u./ml. erythrocytes (chart 2).

Discussion

The carbonic anhydrase activity of each ml. of erythrocytes in the newborn infant averages approximately 60% below the average for normal adult subjects (chart 2). How-

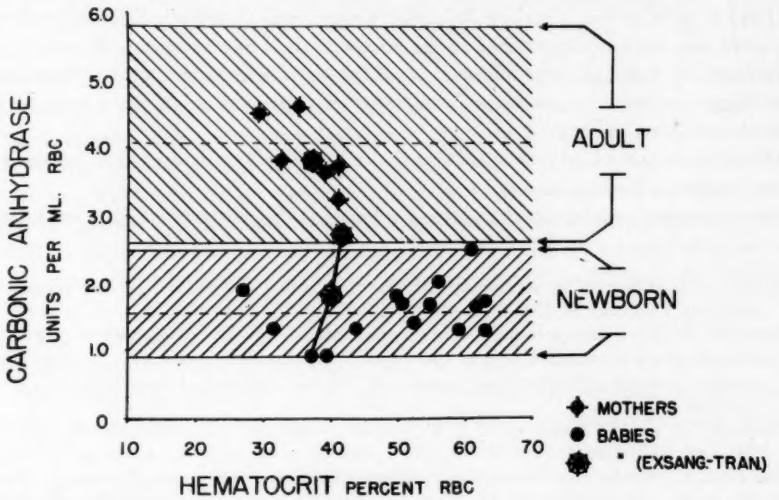

Chart 2. Carbonic anhydrase activity/ml. erythrocytes in adult and newborn subjects. Upper cross-hatched area indicates normal adult range while lower indicates range found in newborn infant; broken horizontal lines are respective averages.

ever, the polycythemia which occurs commonly in the newborn infant, and which may give rise to an increase in erythrocyte mass of as much as 50%, counteracts the effects of this lowering so that the carbonic anhydrase activity of whole blood may be only a little below or even within the adult range (chart 1). Following transfusion with blood from adult donors, the infants' blood carbonic anhydrase level rises to or toward that of normal adult subjects.

It is possible that carbonic anhydrase deficiency as a factor in the physiology of the newborn infant may have been overemphasized. The few data in table 1 relevant to maturity rather uniformly suggest that carbonic anhydrase activity increases before and after birth, but the significance of this to the newborn organism cannot be stated with certainty. While it is known that the enzyme is important in respiratory physiology and that lack of it may possibly be correlated with exertional dyspnea,[8] its precise role in carbon dioxide transport has not been established.[6] Moreover, it is difficult to see how even a considerably greater deficiency than that just reported could in any way interfere with oxygen transport and thus affect the frequency of cyanosis in newborn and premature infants, as has been suggested.[2] The more recent knowledge of carbon dioxide transport in the premature infant[9] would suggest a lower requirement for carbonic anhydrase in such infants. Accordingly, attempts to ascribe physiologic abnormalities which may be seen in the newborn infant to

lack of the enzyme must be regarded as poorly founded.

The blood of mothers at term may show a slight diminution in carbonic anhydrase activity paralleling the degree of anemia which may exist. This finding resembles those seen in most other types of anemia in adult man.[8]

Summary and Conclusions

Each ml. of erythrocytes of newborn infants exhibits carbonic anhydrase activity which, on the average, is approximately 40% of that found in the erythrocytes of adult subjects. The deficiency appears to vary with the maturity of the organism, either *in* or *ex utero*. It is not as great as that described by earlier workers who used methods of less validity. Moreover, the relative polycythemia of the newborn infant counteracts this deficiency, and accordingly the blood of these infants may exhibit carbonic anhydrase activity within or a little below the normal adult range. Transfusion into infants of adult blood increases the carbonic anhydrase activity.

Mothers in whom blood hemoglobin levels are low show similar degrees of lowering of blood carbonic anhydrase activity.

The functional significance of the changes found in the newborn infant is not known.

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Spanish Abstract

La Actividad de la "Carbonic Anhydrase" en la Sangre Materna y en los Recién Nacidos

La actividad de la "carbonic anhydrase" en cada centimetro cubico de eritrocitos de recién nacidos es aproximadamente un 40% de la actividad encontrada en los eritrocitos de los adultos. Esta deficiencia parece variar con la madurez del organismo en utero o ex-utero. Esta deficiencia no es tan grande como la descrita en trabajos anteriores, en los cuales los metodos usados eran menos exactos. Ademas la policitemia relativa de los recién nacidos contrarresta esta deficiencia y por consiguiente la sangre de los recién nacidos muestra una actividad de la "carbonic anhydrase" dentro de los limites normales o un poco mas baja de los valores adultos. La transfusion de sangre adulta a recien nacidos aumenta la actividad de la "carbonic anhydrase."

Se observó que madres con valores bajos de hemoglobina presentaron similarmente una disminucion en el grado de actividad de la "carbonic anhydrase."

La significancia funcional de estos cambios en el recién nacido es desconocida.

300 Longwood Avenue

CONGENITAL DEFICIENCY OF ABDOMINAL MUSCULATURE WITH ASSOCIATED GENITOURINARY ABNORMALITIES: A SYNDROME

Report of Nine Cases

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Buffalo, N.Y., and Easton, Pa.

CONGENITAL deficiency of abdominal musculature with associated genitourinary anomalies is a comparatively rare but easily recognized condition. Thirty-three cases had been reported[1-31] by 1934 when Housden[32] reported his own case and reviewed the literature. Nine additional cases have been reported.[33-39]

From June 1948 to February 1949, the present authors saw six cases, discovered two more in the autopsy files of Babies Hospital, and examined the record of a case in another hospital. This experience suggests that this condition is much more common than heretofore suspected, and has probably been filed in the nondescript classification of "multiple congenital anomalies" instead of being recognized as a syndrome.

The basic elements of the syndrome consist of: (1) partial or complete deficiency of the abdominal musculature, and (2) obstructive manifestations of the genitourinary tract which may take the form of an enlarged bladder without other genitourinary anomalies, or may include bilateral hydroureter and hydronephrosis. Every case except one, including the authors' as well as those in the literature, has been in a male, and in every male except two, the testes were reported to be undescended if they were mentioned at all. Other congenital anomalies have frequently been associated with this syndrome, chief among them being persistent urachus, a pigeon breast deformity of the chest, and some form of talipes.

Even before 1937, when the modern era of chemotherapy of infections may be said to have begun, this syndrome was compatible with long survival. Most patients, however, died of urinary tract infection at an early age. It seems worth while at this time to report these cases, reopen the question of pathogenesis, and reconsider possible treatment in the light of modern antibiotic and chemotherapeutic agents and improved surgical technics.

The following case reports illustrate practically all of the features of the syndrome:

CASE REPORTS

Case 1. T.P. (Fig. 1), a 3½ mo. old Negro male, was admitted to Babies Hospital because of laxness of the abdominal wall since birth and an equinovarus deformity of the right foot, with webbing of all the toes. The testes were not palpable in the scrotum or inguinal canals. There was no deformity of the chest.

Although there were no urinary symptoms or signs, a persistent pyuria was found, which was due to Ps. aeruginosa. The level of blood NPN ranged between 41 and 63 mg./100 cc. during his hospital stay.

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Intravenous pyelography revealed a moderate hydronephrosis and hydroureter on the right. Retrograde pyelography on the left showed the catheter coiled in either a dilated lower left ureter or a hydronephrotic left kidney.

When the child was anesthetized for retrograde pyelography he withstood the procedure so poorly that further surgery was believed to be contraindicated. He was discharged to be followed in the clinic, but shortly afterwards was admitted to another hospital where he has been for almost a year. He has had several episodes of acute pyelonephritis with rise in blood NPN to over 100 mg./100 cc., and it was felt on several occasions that he was about to die. However, he has responded well on

FIG. 1. Case 1, T.P., at 3½ mo. of age, showing flaccidity of abdominal wall with bulging in dependent part. Deformity of right foot is also seen.

each occasion to sulfadiazine, penicillin and streptomycin, and at last report was in good condition with a blood NPN level of 28 mg./100 cc.

Case 2. J.M. (Fig. 2), an 11 mo. old Negro male infant, was transferred to Babies Hospital from another hospital to which he had been admitted 6 wk. earlier because of hematuria of 2 days' duration.

At birth a congenital deficiency of the abdominal musculature was noted, but no other abnormalities were found or suspected. Development was normal except that the child could not sit by himself until he was 11 mo. old. When hematuria occurred at 9½ mo., he was hospitalized and physical examination disclosed, in addition to the defective musculature, masses in the flanks suggesting enlarged kidneys. There was a prominent midline linear crease extending from the umbilicus to the symphysis. Abdominal reflexes were present in all 4 quadrants, greater on the left. The testes were not palpable in the scrotum or inguinal canals.

Initial urine pH was 7.5 and specific gravity was 1.020. There was a 1+ albumin, and the sediment was loaded with white and red blood cells and bacteria, which on culture proved to be B. Proteus. There was no spina bifida or other deformity of the lower spine by roentgenogram. An enlarged bladder was discovered by cystogram, with reflux up the right ureter which was tortuous and dilated. The right kidney pelvis was also dilated. Retrograde pyelography on the left revealed a markedly dilated and tortuous ureter with diffusion of dye into the left kidney region (Fig. 3). This dispersion of dye

was so great that ureteral perforation was suspected initially. Subsequent films showed this to be a huge hydronephrosis (Figs. 4 and 5).

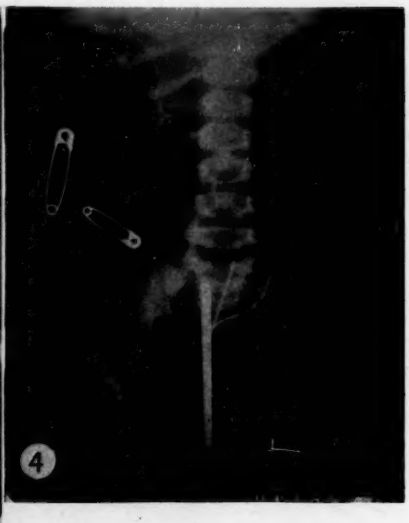
Bilateral nephrostomies were considered, but not performed because it was felt that the prognosis was poor. He was sent home to be followed in the clinic. Three months later, however, he was doing well; he was walking and had had only 1 upper respiratory infection. Accordingly he was readmitted for surgical treatment.

Shortly after admission, the left kidney became acutely obstructed, and left pyelostomy was per-

FIG. 2. Case 2, J.M., at 11 mo. of age. Deformity of abdominal wall is asymmetric, being more marked on right. Note also midline striae.

formed as an emergency procedure. At this time he was exceedingly ill, dehydrated and uremic, but responded well to decompression and intravenous therapy. One month later a right pyelostomy was performed. The following month a resection of the upper third of the left ureter was performed, and the ureter was re-anastomosed to the kidney pelvis after excision of a uretero-pelvic stricture. The following month a similar procedure was carried out on the right side.

Subsequent intravenous pyelography revealed good kidney function on the right, and minimal function on the left with obstruction at the uretero-pelvic junction. However, his blood NPN was 34 mg./100 cc., and he was in good condition, and able to void well through his urethra.



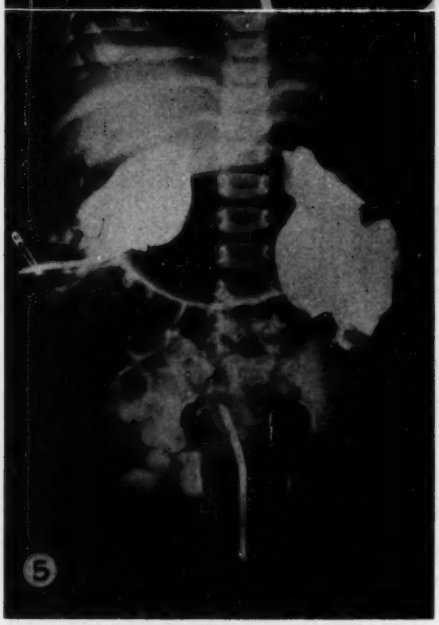


FIG. 3. Retrograde pyelography on Case 2 preoperatively, revealing marked abdominal distention and presence of catheter in hydroureter. Because entire abdomen was not included on this film, ureteral perforation was initially suspected. Later film revealed dye outlining hydronephrotic kidney with tortuous hydroureter.

FIG. 4. Retrograde pyelography on Case 2 revealing catheter coiled in huge hydronephrosis.

FIG. 5. Hydronephrosis in Case 2 demonstrated by pyelography through pyelostomy tubes.

Case 3.* C.E. was born at New York Hospital after full term, normal delivery. Marked laxness of the abdominal wall and gross hematuria were noted after birth. The testes could not be palpated in the scrotum or inguinal canals. A cystogram revealed a large hypertrophied bladder, apparently attached

* Dr. S. Z. Levine, Director of Pediatrics, and Dr. Victor Marshall, Director of Urology, New York Hospital-Cornell Medical Center, kindly gave the authors permission to report this case which was treated on their pediatric service.

to the anterior abdominal wall by a urachus which appeared closed at the umbilical end. Reflux of dye up the ureters revealed bilateral hydroureter and hydronephrosis.

When the patient was 3 wk. old, bilateral nephrostomy was performed, at which time it was noted that there were 3 thin muscular layers in the flanks, and that the right kidney was larger than the left, but not dilated or thin.

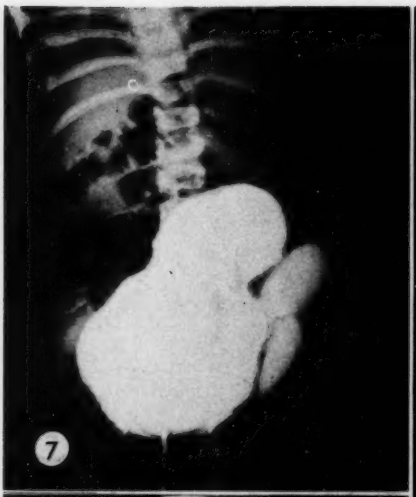
Three weeks later the lower 7 or 8 cm. of the left ureter were resected with reimplantation of the upper segment into the bladder, which was then drained by suprapubic cystostomy. The ureter was large and tortuous and had entered the bladder anteriorly near the midline. Nerve fibers were present

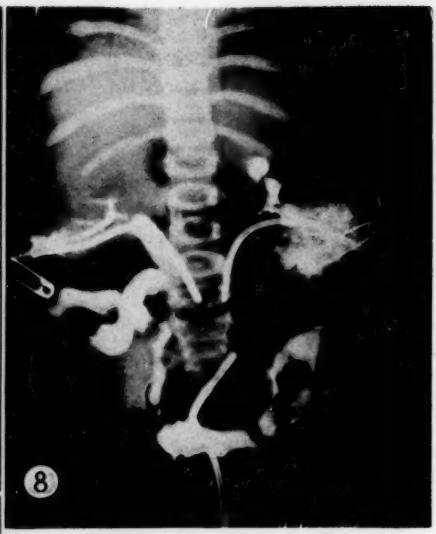
FIG. 6. Case 4, at 2 yr. of age, after all surgical procedures.

and hypertrophy of the muscle layers in the resected ureteral segment were noted on microscopic examination. The bladder was enlarged and its wall thickened. The infant tolerated the procedure well, and pyelography through the nephrostomy tube 2 wk. later showed a functioning ureter and good improvement in the hydroureter.

One month later, a partial (8 to 10 cm.) resection and reimplantation of the right ureter into the bladder was performed. The following week a right pyeloureterogram showed marked postoperative improvement in the hydroureter. The child was discharged at the age of 4 mo. with a suprapubic cystostomy tube in place. At the time of discharge he was able to void through the urethra without difficulty, but it was felt advisable to leave the cystostomy tube in place until the ureters and kidneys had had ample opportunity to regain maximum function. Urinary infection was controlled by sulfadiazine, occasionally augmented by penicillin.

At the age of 1 yr., or 9 mo. after the right nephrostomy tube had been removed, intravenous pyelography demonstrated considerable improvement in both ureters, some improvement of the left kidney, and no change in the right kidney. Blood urea nitrogen was 16 mg./100 cc. Phenolsulphonephthalein excretion was 60% in 2 hr. and urea clearance was 32% of adult standards on 1 occa-





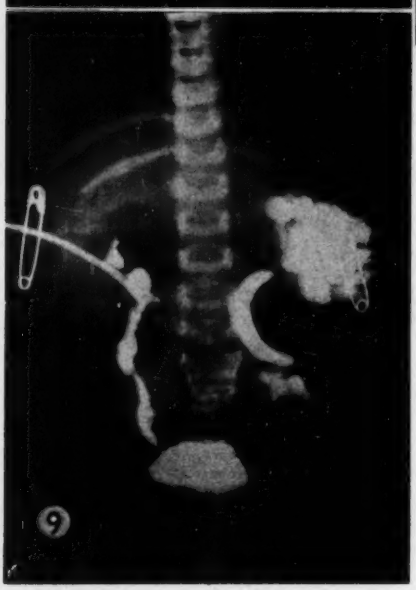


FIG. 7. Cystogram on Case 4 showing hourglass deformity of bladder and reflux up tremendously dilated ureters.

FIG. 8. Pyeloureterogram on Case 4 after bilateral pyelostomies had been performed and prior to resection of redundant loop of right ureter.

FIG. 9. Pyeloureterogram on Case 4 after right ureteroplasty.

sion. The child wore a tight abdominal binder and had developed normally and was able to walk a few months later.

At 23 mo. of age, he was readmitted because of acute enteritis. After his recovery from this infection an intravenous pyelogram was done which showed good function on both sides in 10 min. There was minimal dilatation of both kidneys and upper ureters, a marked improvement over previous pyelograms. Accordingly the cystostomy tube was removed and the wound healed uneventfully. A subsequent pyelogram 3 mo. later was interpreted as showing excellent function with a 1+ hydronephrosis on the right and an essentially normal pyelogram on the left. Blood urea nitrogen was 16 mg./100 cc. and phenolsulphonephthalein excretion was 4% in 30 min., 40% in 60 min. and 50% in 2 hr. His abdomen continued to be relaxed and dependent in the flanks when he assumed the

supine position. This dependency required that he wear a corset for comfort, and to make defecation easier.

Case 4. R.V. (Fig. 6), a white male, was 15 mo. old when hospitalized because of fever and deficient abdominal musculature, which had been noted at birth. One month prior to admission, he developed pneumonia and continued to suffer from anorexia, irritability and intermittent episodes of fever. There were no urinary symptoms.

The most striking feature of the physical examination was a lax abdomen which had a midline linear crease from the symphysis to the umbilicus. The bladder was palpable half way to the umbilicus. The testes were not present in the scrotum or inguinal canals. There was a pigeon breast deformity of the anterior thoracic cage.

A cystogram (Fig. 7) revealed a capacity of over 400 cc., and the bladder was hour-glass in shape. There was reflux up the left ureter. RG of the lower spine showed no abnormalities. Obstruction at the bladder neck by a fibrous bar was noted cystoscopically.

There were several episodes of pyelonephritis which were controlled with sulfadiazine and penicillin. Then a left nephrostomy was performed, followed 1 wk. later by a right nephrostomy. A pyeloureterogram (Fig. 8) demonstrated a redundant loop of right ureter which was then excised with reanastomosis. A postoperative pyeloureterogram (Fig. 9) showed a good functioning ureter. One month later the redundant left ureter was excised and the upper segment reimplanted into the bladder. At that time a suprapubic cystostomy was also done, and a large wedge of fibrous tissue was excised from the posterior bladder neck. Three weeks later, after having been clamped for a week, both nephrostomy tubes were removed. Shortly afterwards the suprapubic tube was removed and all wounds healed uneventfully. Ten days later, however, he again became febrile, and catheterization disclosed continued obstruction at the bladder neck. A transurethral resection of the bladder neck was then performed, but retention continued. Cystometric studies revealed a completely atonic bladder with a 350 cc. capacity. Suprapubic cystostomy was repeated in the hope that with adequate drainage bladder tone would eventually develop.

Case 5. M.L. was first admitted to Babies Hospital when he was 2 yr. old because of abdominal distention since birth, hypospadias and undescended testicles. At 1 yr. he had been fitted with a corset in order to aid in defecation. One month prior to admission RGs were made in an effort to determine the cause of the relaxed distended abdomen, and when it was noted that he had an enlarged right kidney he was referred to Babies Hospital for further investigation. There were no urinary symptoms.

Physical examination revealed a well developed and nourished white male who stood with his back arched to support his distended abdomen. The chest was flattened in the anteroposterior diameter with flaring of the costal margins, flattening of the sternum, and some retraction of the xiphoid. There was a loud blowing systolic murmur in the aortic area which was transmitted towards the apex. The abdominal muscle tone was poor, and when the patient lay on his back the abdominal contents became dependent in the flanks. The testes were undescended and could not be felt in the inguinal canals. There was mild hypospadias.

Urinalysis was normal. The blood NPN was 35.4 mg./100 cc. Intravenous pyelography showed a dilated right kidney pelvis and a dilated and tortuous right ureter. A small amount of dye on the left side was seen only on the 40 min. film. The bladder was enlarged and after voiding there was still considerable dye left in the bladder. Cystoscopic examination disclosed a normally placed left ureter which was catheterized, and a mass on the right with a small dimple which could not be catheterized.

It was felt that he had a left hypoplastic kidney, and a right hydronephrosis and hydroureter secondary to partial obstruction at the right uretero-vesical junction.

He was discharged from the hospital after this work-up, but had to return shortly because of fever and the appearance of pus in the urine. B. Proteus was cultured from the urine at this time, and the infection responded well to sulfadiazine.

The bladder was then explored through a suprapubic incision. A stricture of the right ureteral orifice within the bladder wall was found. An incision was made through the bladder wall about 2 cm. above the right ureteral orifice, and the ureter was brought into the bladder opening, incised, probed and sutured to the bladder wall. A wedge-shaped section of the posterior bladder neck measuring 5 x 5 mm. was excised in order to relieve partial obstruction due to median bar fibrosis.

Postoperatively he did well, but shortly after discharge he developed a pyuria which required

readmission. The urethra was dilated, and he was given streptomycin to control the B. Proteus urinary infection.

He has had to be readmitted 3 times for recurrent pyelonephritis that has always been due to a nonhemolytic streptococcus. This organism was found to be resistant to sulfadiazine. On his last admission at the age of 5 yr., he was treated with bacitracin, to which the organism was sensitive, and his urine was sterilized within 5 days. He was discharged in excellent condition following this treatment. The left kidney was still considered hypoplastic, but there had been some improvement on the right side.

Comment: It is of interest that this syndrome was not recognized as such in this patient until his fifth admission, at which time the patients described as Cases 2 and 4 were also on the ward.

Case 6. C.C. (Fig. 10), a full term, white male infant, was born at home by breech presentation 1 wk. prior to admission to Babies Hospital. Because his abdomen was lax and large, he was brought to the hospital.

The most striking feature of the physical examination was the appearance of the abdominal wall, which was like a loose, asymmetric sack, extending far out to the right. On gentle lower abdominal pressure, urine could be expressed from the lower margin of the umbilicus. The umbilical cord was attached and moist. The testes were not present in the scrotum or inguinal canals, and there was a

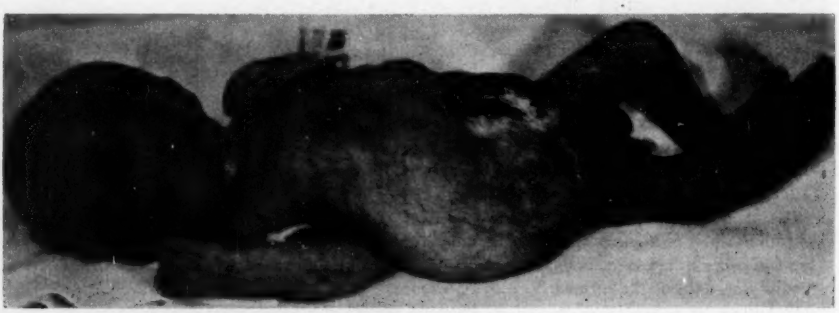


FIG. 10. Case 6 showing flaccid abdominal wall extending far to right and becoming dependent in flank. Cord is still in place and urine leaked from umbilicus. Note deformity of right foot.

mild right talipes equinovarus. The child appeared moderately dehydrated but otherwise in good condition.

Urine was alkaline and contained 3 + albumin, occasional WBC and RBC. Specimen was obtained from the umbilicus. Intravenous pyelogram showed no evidence of excretion of the dye.

The patient was afebrile but listless and feeble during the next 4 days. At no time did he void by way of the urethra. The urachus remained patent. On the fifth day after admission his temperature rose to 38.3° C. and he died.

Postmortem examination disclosed a cystic urachus, 3 cm. in diameter, directly behind the umbilicus connected to an hypertrophied bladder. Just above and behind the urethral orifice there was a sulcus 8 mm. in diameter, which formed a blind pouch about 1 cm. deep lying between the urethra and the rectum. The position was such that the pouch, when filled, might have compressed the urethra.

Passing upwards and laterally on both sides of the bladder were 2 thick, coiled ureters measuring up to 3 cm. in diameter. The right kidney was hydronephrotic with numerous abscesses measuring up to 2 cm. in diameter. The pelvis of the left kidney was only slightly dilated. The testes lay within the abdominal cavity, adherent to the distended ureters.

Dissection of the abdominal wall showed an area measuring 13 x 11 cm. extending from the umbilicus to points 2 cm. from the iliac spines, where there was no muscle. Strands of the recti and the 3 layers of abdominal muscles were found near their origins and insertions. That portion of the abdominal wall which contained no muscle was composed only of skin, subcutaneous tissue and peritoneum.

Case 7. K.F. (Fig. 11) was first admitted to Babies Hospital at the age of 5 wk. because of infection of a persistent urachus.

Pathologic physical findings were limited to the abdomen and genitalia: the abdomen was greatly enlarged and flabby, and its wall was thin and flaccid, apparently having no muscle in it. From a point where the umbilicus should have been there were several scar-like creases radiating down and laterally, and the umbilicus was replaced by an elliptic opening through which urine could be expressed when the lower half of the abdomen was pressed.

A tight foreskin over the glans penis could not be fully retracted,, and the urethral meatus ap-

FIG. 11. Case 7. Note creases below umbilicus which have been described frequently in literature and were also present in Cases 2 and 4.

peared inflamed. The testes could not be felt in the scrotum or inguinal canals. The child was able to void through his urethra, but most of the urine was passed through the patent urachus.

First attempts at catheterization were unsuccessful because of an obstruction encountered about 3½ cm. from the meatus. A filiform sound was then passed, and the urethra dilated, and after several dilatations the urethral stream increased in size and the urachus closed. He was discharged 1 mo. after admission.

Following discharge this patient did very well and had no urinary difficulties. On 3 occasions he received urethral dilatations. After the third dilatation at 6 mo. of age he became anuric and was apparently in pain. He was therefore readmitted. Operation revealed a Staph. albus peritonitis, from which he died 24 hr. after operation.

Postmortem examination revealed a thin layer of muscle in the abdominal wall below the costal margin, but incisions through the middle and lower abdominal walls at different levels failed to show muscle tissue. The anterior wall of the bladder was firmly adherent to the anterior abdominal wall, and the fundus lay at the level of the umbilicus. Part of the omentum was attached to the fundus of the bladder.

The right kidney was normal but the right ureter was dilated to a diameter of 1 cm. at its widest point and was very tortuous. The left kidney showed some hydronephrosis and the ureter was also dilated, thick and tortuous, with considerable variation in its width. Both uretero-vesical orifices were patent.

The bladder was large and thick walled. At its apex in the region of the umbilicus and adherent to the site of the umbilical scar was a firm pyramidal mass, 6 mm. in its greatest diameter, which appeared to be the urachus.

Considerable submucous hemorrhage was present in the walls of the bladder, and in 2 places in the posterior wall of the fundus there was ulceration and thinning of the bladder wall. Through 1 of these ulcers a recent perforation was noted to which the omentum was adherent.

Both testes lay above the pelvic brim. The usual lobes of the prostate were not found. The urethra measured 2 mm. in diameter and was not apparently obstructed. There was marked peritonitis.

It was felt by the pathologist that the bladder perforation was probably secondary to infection rather than to instrumentation because of the presence of the second area of thinning which had evidently been about to perforate at some previous period. All normal vesical structures at that site were replaced by fibrous tissue and the omentum was adherent to the overlying peritoneum.

Case 8. B.C. was born by breech delivery, and Piper forceps were used to assist the aftercoming head. He weighed 2640 gm. and lived only 5½ hr.

The mother's first pregnancy terminated in an incomplete abortion at 10 wk.' gestation, requiring subsequent dilatation and curettage. During this second pregnancy there were 2 episodes of bright red spotting during the first trimester, but no known illness.

Shortly after birth the infant was dyspneic, cyanotic, gray, and in critical condition. The most remarkable physical finding was a very lax abdomen with practically no tone. The heart rate was slow and there was a systolic murmur. There was marked equinovarus deformity of the feet.

At necropsy a cyst 10 cm. in diameter was found fixed to the abdominal wall just below the umbilicus, which communicated with bladder and was presumed to be urachus. The bladder was enlarged and thickened. There was no urethral orifice in the bladder. An attempt to probe the urethra from the penile end met with complete obstruction at the bladder outlet. The testes were in the abdominal cavity.

The right kidney was cystic and small. The right ureter was enlarged up to a diameter of 0.8 cm., tortuous, thick walled, and entered the bladder normally. The left kidney was cystic and hypoplastic. Its ureter was also enlarged, thickened, tortuous, and entered the bladder normally.

All the abdominal muscles were present. Microscopically there was variation in the size of the muscle fibers, with occasional large fibers where striation was absent.

In addition there were bilateral tentorial tears with subdural hemorrhage, and some epidural and meningo-arachnoid hemorrhage of the cord.

Comment: In an infant who dies at 5½ hr. and is in shock most of the time, it would not be surprising to find an abdominal wall with practically no tone. This, combined with the pathologic report of normal appearing muscular layers may make one wonder whether the authors are justified in reporting the case as an example of this syndrome. However, the abdominal wall in this case was exceedingly relaxed and baggy, and appeared as though it had been excessively distended for long periods in the past. It suggested that genitourinary pathology would be found to go along with it. Furthermore, the muscle deficiency may be only functional, although in many cases parts of the muscles or even the entire musculature may be completely absent.

It becomes even more difficult to justify inclusion of the following case because functional deficiency cannot be demonstrated in a stillborn, and there were no anatomic changes in the muscles. Furthermore, it is the only other case where the testes were in the scrotum.

However, again the pathologist suspected that the genitourinary abnormalities would be found after he had looked at the abdominal wall, and this suspicion was borne out by the findings. The case is included to emphasize the point that defective-appearing abdominal musculature demands genitourinary investigation.

Case 9. A stillborn infant was delivered with much difficulty due to shoulder impaction. The

abdomen was tremendously enlarged and bulged out from the bony structure of the chest and pelvis on each side as if there were no supporting musculature. A fluid wave was present. When pressure was exerted on the abdomen, straw-colored fluid oozed from the umbilicus.

There were 150 cc. of free serosanguineous fluid in the peritoneal cavity. Both kidneys were slightly enlarged and hydronephrotic. The parenchyma was only 0.5 cm. in thickness. Tiny pin-point cysts studded much of the external surface of both kidneys. A large cyst of the left kidney was torn away when the capsule was removed.

Both ureters were enlarged and tortuous, measuring 0.6 cm. in diameter in the collapsed state, and entered the bladder normally.

The bladder was enlarged and thickened. The prostatic urethra was enlarged, and the wall hypertrophied and thickened to 0.5 cm. The dilatation and hypertrophy ceased abruptly just below the verumontanum where a semicircular curtain-like membrane attached to the anterior wall and to each side of the urethra practically occluded it. The free semilunar edge was directed cephalad and posteriorly. Distal to this point the urethra was normal. The arrangement was such that catheterization would have been easy, but urinary flow in the opposite direction would have been difficult if not impossible. The testes were in the scrotum, and there was bilateral hydrocele.

The immediate cause of death was complete separation of the vertebral column between the second and third cervical vertebrae, with fragmentation of the third vertebra.

Review of the Literature

Forty-two cases have been reported in the literature. Many of the reports are incomplete, particularly those of patients who were living at the time of the report or where no autopsy was performed. This is in large part due to the fact that modern diagnostic methods were not available.

Every case except one[25] was in a male. Twenty-eight out of the 42 died, at ages ranging from a few hours to 3 years. Autopsy was performed in 21. The cause of death was usually infection, pneumonia being specified in six instances. Uremia was mentioned twice. The remaining 13 patients were still living at the time of report, 4 being less than 1 year, 9 at ages ranging from 2 to 70 years.

No unusual features have been noted in the family or obstetric histories to suggest the pathogenesis of the condition.

The abdominal musculature varied from complete absence microscopically, to the macroscopic presence of all layers which were merely thin. Several of the cases showed no clinical evidence of functioning muscle. They could not be stimulated to contract voluntarily, reflexly or electrically. Often the origins and insertions of these muscles were present and found to diminish in size and finally disappear in the area overlying the bladder. The bladder was grossly enlarged in every autopsied case except one, and clinically enlarged in 10 additional cases. Housden[32] concluded that failure to mention the bladder could not be taken as evidence that the bladder was normal in size.

There was some degree of dilation of one or both ureters in every autopsied case except one, and in most of them the dilatation was enormous, simulating small intestine. Obstruction of the ureters was frequent either at the uretero-pelvic or uretero-vesical junctions. Occasionally there was atresia along the course of the ureter.

There was bilateral hydronephrosis in 10 autopsied cases, and unilateral hydronephrosis in five. In four instances one kidney was atrophic. There was one case of bilateral polycystic kidneys. In all the other autopsied cases, evidence of some form of kidney damage was found except in two which were reported to be normal. In the cases where no autopsy was performed, unilateral hydronephrosis was demonstrated twice, once by operation and once by pyelography. In two cases the kidneys were enlarged to palpation. In the remaining cases no information is available.

The testes were not in the scrotum or inguinal canals in every case where they were

mentioned except one.[1] They were found in the abdomen in every autopsied case.

The urethra was described as unobstructed in nine cases, and was not mentioned in any other case until Housden demonstrated a median bar in his cases. Since then Howard[36] found one case in which the urethra was completely obstructed. In the case reported by Daut, Emmett, and Kennedy[37] there was a vesical neck obstruction which was relieved by resection of 3 gm. of tissue from the bladder outlet. Emmett reported in 1949[38] that this patient was still doing well, but that the left kidney had never been visualized and was believed atrophic. Obrinsky[39] reported valvelike folds in the prostatic urethra, and a saccular dilatation of the penile portion of the urethra. In addition there was phimosis which required a dorsal slit. This would suggest that urethral obstruction was or had been present in spite of the ease of catheterization.

In nine cases a urachus was present, or the bladder was adherent to the umbilicus. The urachus was patent twice.

There was a pigeon breast deformity of the chest in 16 cases, with a Harrison's groove coexisting twice. In two other cases Harrison's groove was present as the only chest deformity. Some form of talipes was noted in six cases. No other deformities were reported more than once with the exception of inguinal hernia, which occurred twice. Hirschsprung's disease, idiopathic dilatation of the colon, was reported in one case.[21]

The present authors' nine cases show most of the features of those in the literature. All are male, all have enlarged bladders and bilateral hydroureters. Eight out of nine have undescended testes, three have bilateral hydronephrosis, five have unilateral hydronephrosis, one living child has one kidney which has never been visualized and is presumed to be atrophic, and one patient who died had one atrophic polycystic kidney.

Five of the 9 patients are living; and of the 4 fatal cases, one was stillborn, one died shortly after birth, one at 2 weeks of age, and the other at 6 months. Four of the remaining 5 have been treated by various surgical methods, and are at present doing well.

In 5 of the 9 cases a urachus was present, and in 3 of these the urachus was patent.

The most striking difference between the present authors' cases and the cases in the literature is the presence of urethral obstruction in 5 out of 9 cases. In two cases median bar fibrosis was seen at operation and resected. One of these had a wedge of tissue removed when cystotomy was performed, and two subsequent transurethral resections of the vesical neck were required. In one case the urethra had to be repeatedly dilated before the patent urachus would close. In two cases there were blind urethral pouches capable of obstructing urine flow when they were filled. Complete urethral atresia was present once.

Pathogenesis

Although congenital anomalies are frequently multiple, the fact that genitourinary anomalies can be predicted once the abdominal muscles have been seen to be defective has led observers to suspect that the two features are causally related; and in the literature the belief is sometimes stated that the muscle defects are secondary somehow to the genitourinary anomalies, at other times vice versa.

The theory accepted by most authors is that advocated by Stumme[8] in 1903, which postulates that the bladder becomes obstructed in utero either at or distal to the vesical neck after the upper end of the bladder has lost its communication with the allantois. Subsequently, urine collects in the bladder, causing distention, with secondary ureteral dilatation and hydronephrosis. As the bladder enlarges it presses against the abdominal wall and

causes atrophy of the muscles, either by direct pressure or by interference with their blood supply. Descent of the testes, a later embryologic event, is prevented either by obstruction from a large bladder or by obliteration of the inguinal canals. By the time the infant is born it is presumed that the obstruction at the bladder outlet or the urethral obstruction has been overcome, so that frequently no mechanical obstruction is apparent after birth.

In support of this theory are these facts: 1. The missing muscles in order of frequency are the transversus, obliques, lower recti, and finally upper recti. In other words, the muscles are destroyed from within outwards, and more completely in front of the bladder area. Remnants of the origins and insertions are frequently detectable grossly and microscopically near the ribs and iliac crests.

2. In no reported case can we be sure that abdominal muscle deficiency was present in the absence of an enlarged bladder.

3. The abdominal wall at birth shows obvious evidence of long-standing distention which could be accounted for only by an enlarged bladder, or perhaps by intrauterine ascites which clears prior to delivery.

4. The presence of a short urachus in 14 cases, patent in five, suggests that lower urinary obstruction might have been a cause of the persistence of this structure. Such a postulate would require modification of Stumme's theory and make it necessary to assume that the urinary obstruction occurred prior to the obliteration of the allantois or at about the same time.

5. Dilatation of the upper genitourinary tract is usually due to obstruction. Urethral obstruction has been present in over 50% of the cases reported since Housden emphasized the importance of looking for the obstruction, which frequently is not obvious. The fact that every case except one has occurred in a male lends support to the theory that the site of obstruction is in the urethra, this being common in males and uncommon in females. Frequently obstructive manifestations in the genitourinary tract are ascribed to "neuromuscular imbalance," a vague classification used to disguise our ignorance of the basic pathology in the absence of morphologic changes in either the muscles, nerves or central nervous system. It has been suggested that such a mechanism might be operating here, as careful nerve dissections and spinal cord cell counts have failed to reveal any abnormality.[9,11] The case reported by Daut, Emmett, and Kennedy from the Mayo Clinic[37] with marked improvement effected by transurethral resection of the vesical neck in the absence of apparent organic obstruction tends to support this theory. In their case, following resection of 3 gm. of material, an initial residual urine of 400 cc. was reduced to zero, with no loss of sphincter control.

The two arguments against Stumme's hypothesis are: 1. There are numerous case reports of congenital obstructive uropathy without defect in the abdominal musculature. Howard[36] suggests that this is because the obstruction occurs later in the embryologic development, after the muscles have already formed.

2. In certain cases no trace of abdominal musculature was found, which speaks for congenital absence rather than for pressure atrophy or fetal muscular dystrophy. And one pathologist, Batten (quoted by Garrod and Davies[9]), felt that the microscopic picture of the residual muscle tissue suggested failure of development, not atrophy.

A second theory proposes that the urinary malformations are secondary to the abdominal musculature deficiency. These proponents state that the abdominal muscles are essential muscles of micturition, and that when they are absent the bladder cannot be completely

emptied and tends to expand rather than contract because of the lack of resistance usually afforded by the abdominal wall. The original defect is presumed to be either a failure of the myotomes to descend into the ventral wall,[20,28] or a failure of the myotomes to fuse anteriorly. Primary atrophy is favored by some, no cause being suggested.

The present investigators consider Stumme's theory more probable, particularly now that genitourinary obstruction is being found since Housden emphasized the importance of a thorough search for it. However, the very real possibility that there is no cause and effect relationship awaits further embryologic knowledge.

Prognosis and Treatment

The syndrome is compatible with survival to old age, one case being reported at 70 years.[13] However, most of the patients reported have died in the first year, the commonest cause of death being infection, such as pneumonia, bacteremia and pyelonephritis. With modern chemotherapeutic and antibiotic agents many of the reported immediate causes of death can be controlled, and we are left with the genitourinary anomalies and the mechanical problem of abdominal support, the management of constipation, postural defects and difficulty in learning to walk.

A corset has helped in these latter conditions. One infant learned to walk almost immediately after such support was provided.[28] Defecation becomes easier and thus the constipation tends to become alleviated.

Ultimate prognosis depends on the degree of kidney function present at birth, on urinary infection and on the time of institution of urologic treatment. The wide range of such treatment in the reported cases indicates that probably all methods of treatment leave something to be desired. The paucity of reported cases has undoubtedly contributed to the multiple methods of therapy. However, there are certain features which deserve emphasis.

First, recognition of the muscular defect, which is usually easy, makes immediate investigation of the genitourinary tract mandatory, regardless of the absence of urinary symptoms, because symptoms are usually not present. This is perhaps the most important lesson to be learned from past experience. Too often investigation of the urinary tract has been delayed until no therapy could offer any hope.

A cystogram will frequently be the most valuable diagnostic test, often outlining not only the bladder but also the ureters and kidney pelves. However, a cystogram without reflux up the ureters must not be considered to rule out hydroureter or other upper genitourinary abnormality because of the frequency of uretero-vesical obstruction. Intravenous pyelograms are usually unsatisfactory in infants, and when hydronephrosis and hydroureter provide marked dilution of the dye, satisfactory visualization is almost impossible.

The most important therapeutic measures are those directed toward relief of obstruction and urinary stasis, in order to prevent or clear up any infection. Antibiotics alone without free urinary flow are of only temporary value. Not only does the infection persist, but strains of the infecting organism may become resistant to the antibiotic, thereby limiting the effect of such medication at a later date.

Whether nephrostomy, pyelostomy, ureteroplasty, uretero-vesical reimplantation, or merely a resection of the vesical neck is required will depend on the individual situation. The important factor is that the need for such procedures be recognized early, and that they be performed as soon as possible before the kidneys are irreparably damaged.

Summary

Nine cases of congenital deficiency of the abdominal musculature with associated genito-urinary abnormalities are presented, the literature is reviewed and the pathogenesis and treatment are discussed.

It is emphasized that when congenital deficiency of the abdominal muscles is recognized, particularly in a male infant with undescended testes, or when there is a patent urachus, obstructive manifestations in the genitourinary tract must be searched for and corrected at the earliest possible moment. Urinary symptoms in these cases are usually not present.

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SPANISH ABSTRACT

Sindrome de Deficiencia Congenita de la Musculatura Abdominal Asociada con Anormalidades Genito-urinarias; Reporte de Nueve Casos

Se presentan nueve casos de deficiencia congenita de los musculos abdominales con manifestaciones obstructivas genito-urinarias asociadas. Este sindrome generalment ocurre en varones y los testiculos invariablemente están en el abdomen. Otras anomalias frecuentemente encontradas son: la persistencia del uraco, deformidad de "pecho de paloma" y talipe equinovarus.

El grado de deficiencia muscular varia entre una ligera debilidad, a su ausencia completa, facilmente reconocida al nacimiento. Cuando este defecto muscular es reconocido, es necesario hacer una investigacion extensiva del aparato genitourinario, debido a que todos los casos reportados presentaron por lo menos una dilatación de la vejiga, o una hidronefrosis con hidroureteres. En la mayoria de los casos recientemente reportados, se demostró una obstruccion ureteral y en los otros casos restantes sin obstruccion demostrable, se sugiere como causa, la presencia de un "imbalance neurogenico." Los autores estiman que los defectos musculares son secundarios a las obstrucciones urinarias ocurridas en utero.

El tratamiento en estos casos debe ser dirigido a la correccion temprana de la obstruccion y estasis urinario.

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TOTAL BLOOD EOSINOPHIL COUNTS IN THE NEWBORN PERIOD

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RECENT investigation has demonstrated a fall in total blood eosinophil count as a response of the body to stress or to a sudden release of adrenal corticosteroids into the blood stream. This fall occurred within four to six hours, but recovery to the control level was less abrupt and required two to four days.[1] The changes in total eosinophil count in response to the stress of birth have been recorded for mothers,[2] but not for their newborn infants. In this study serial determinations of total eosinophil counts were undertaken in a series of newborn infants.

METHOD

Eosinophil counts were done by the method described by Forsham et al.[3] in 0.2 mm. deep Fuchs-Rosenthal chamber. Determinations were made on fresh capillary blood. A free flow of heel blood from the puncture wound was necessary to obtain reproducible results. Counts were done at approximately 24 hr. intervals during the infant's nursery admission and were repeated at approximately 1 mo. of age. The initial determinations were made in the 1st 12 hr. of life on infants born between the hours of 6 A.M. and 10 P.M. Except for this time limitation the sampling of infants was random. It was not possible to control the time of the counts relative to feedings.

RESULTS

The mean values and ranges of total eosinophil counts at birth, 1 month, and 2 to 10 months of age are presented in table 1. In a group of 30 infants there occurred a

TABLE 1

Age range	No. of cases	Total eosinophil count/mm.^{3}	
		Mean	Range
Birth (0–12 hr.)	42	267	19– 851
1 mo. (25–33 days)	30	483	156–1150
2–10 mo.	15	248	69– 571

mean rise of 222 eosinophils from birth (0 to 12 hours) to 1 month of age. The standard error of the difference was 40.1; the value of t was 5.54. Since this increment might have represented the recovery from a period of physiologic stress (i.e., birth), the eosinophil counts at age 5 days were compared to the follow-up counts at 1 month of age. Twenty-eight infants at a mean age of 133 hours exhibited at 30 days a mean rise of 143 eosinophils/cmm., with the standard error of the difference being 42.5 and t equalling

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3.37. Both these values for t gave a probability of well over 1 in 100 that these rises were significant and not due to chance sampling.

Serial eosinophil counts were done on 44 infants during the first 5 days of life. In 30 of these infants the total eosinophil counts rose significantly within that period (plus 70 or more); 9 exhibited a fall of 70 or more; and 5 remained the same (i.e., plus or minus 70). These results indicated a significant increase in the total eosinophil count in the majority of infants, not only in the first 5 days of life, but also from the 5th to 30th day.

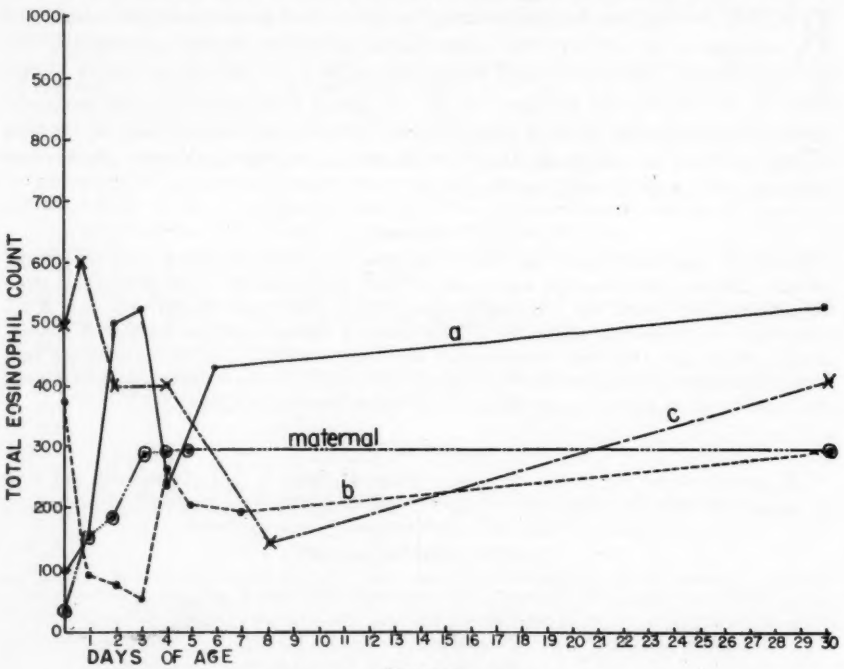

CHART 1

Curves of serial eosinophil counts of each infant related to age demonstrated three patterns. The commonest (chart 1, curve a) exhibited a rise in eosinophil count between 24 to 72 hours of age, followed in the next 48 hours by a significant fall to a level which was usually above that at birth. The count rose subsequently either during the remainder of the infant's nursery admission or at a follow-up visit a month later. In the second type of curve (chart 1, curve b) an immediate and sustained fall for the first 24 to 72 hours was followed by a significant rise. The third type was nondescript and followed no definite pattern (chart 1, curve c). Of 42 curves studied in the first 5 to 7 days of life, 29 were of type a, 11 of type b and 2 of the nondescript type c configuration. These curve types showed no significant correlation with the following factors: race, sex, birth weight, length of labor, birth trauma, neonatal apnea, sedation of mother before birth. Simultaneous eosinophil counts and hemoglobin levels in 10 infants failed to demonstrate that dehydration was a factor in these changes in eosinophil counts. Chart 2 is a composite curve of the average of the daily eosinophil counts of 24 infants.

Series of eosinophil counts were done concomitantly on 10 infants and their mothers. The mean count of the 10 infants at birth was 267, of their mothers 19. Six of these infants showed the type a curve and 4 the type b curve. The eosinophil curves for the 10 mothers were all identical, with an abrupt rise within the first 48 hours and the attainment of a fixed level almost always within 48 to 72 hours. These maternal curves (chart 1, maternal curve) were similar to those recently reported by Davis and Hulit.[2] At one month after birth the mean count for seven babies was 446 as contrasted with 150 for their mothers.

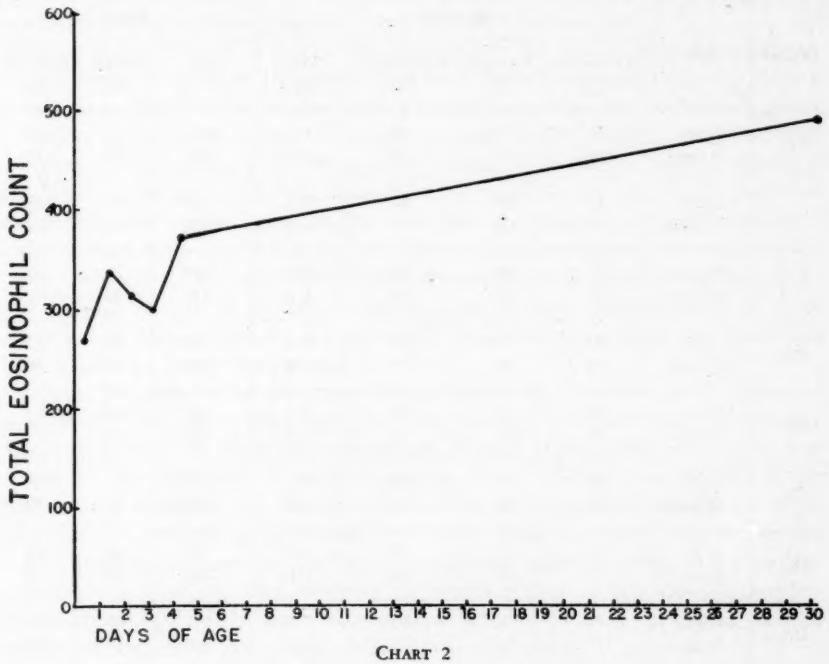

CHART 2

Eleven infants were followed with tibial bone marrow and routine peripheral blood counts in addition to eosinophil determinations. Table 2 shows the marked reciprocal changes in polymorphonuclear and lymphocytic elements in both blood and marrow which occurred in the one month interval after birth. The marked increase in lymphocytes and the definite reduction of rubrocytic elements in the marrow were striking.

DISCUSSION

Changes in total blood eosinophil count can be influenced by a variety of agents. A fall in circulating adrenal corticosteroids might have caused the sharp rise in eosinophils demonstrated in the first three days of life, and might itself have been the result of any of the following mechanisms: (1) a recovery phase from the alarm reaction occurring at birth; (2) the infant's excretion of an excess of maternal corticosteroids; (3) a true physiologic decrease in function of the infant's adrenals from a state of relative hyperadrenalism prior to birth. This increase in eosinophil count might also have resulted from

undetermined, nonspecific growth and fluid alterations occurring in the newborn period. Either of these two concepts might well have explained the usual rise in eosinophil count in the first few days of life.

During the time interval from 5 to 30 days of age, growth or fluid factors operating to influence eosinophil count should have been of much less importance than in the immediate

TABLE 2

Patient	Age	Marrow				Blood		
		Myelocytic (%)	Lymph (%)	Rubrocytic (%)	Eos. (%)	Eos. (total)	Polys. (%)	Lymphs (%)
Tt.	110 hr.	77	3.6	13	2.3	340	60	31
	29 days	31	46	16	2.0	524	18	78
Cy.	1½ hr.	53	16	24	4.0	619	59	35
	25 days	24	62	1	4.3	1026	23	62
Nr.	51 hr.	70	10	16	3.0	399	74	18
	30 days	36	35	14	4.3	436	25	71
Gn.	1½ hr.	34	8.6	50	2.3	226	70	24
	30 days	24	54	10	6.6	249	28	78
Ps.	108 hr.	68	7	21	3.3	247	63	24
	28 days	26	61	4	1.0	287	30	63
Hn.	10 hr.	49	11	34	2.3	225	65	25
	34 days	33	36	19	2.0	318	34	59
Cs.	32 hr.	57	13	23	3.0	530	66	26
	26 days	24	58	12	2.0	762	14	78
Dm.	106 hr.	77	8	10	1.3	177	38	57
	21 days	27	54	7	3.0	160	18	71
Fd.	5 hr.	57	8.0	31	2.6	75	64	26
	27 days	16	69	7	5.0	520	25	69
Gs.	5 hr.	57	13	21	5.9	365	71	20
	30 days	39	45	9	2.3	1150	31	65
Gis.	1 hr.	60	10	26	2.3	400	73	19
	30 days	31	47	9	2.3	321	29	66

newborn period; but they remained as a possible explanation of the almost constant rise in eosinophil count during this period. The changes in neutrophil and lymphocyte counts noted at birth in both blood and marrow constituted a complete hematologic picture associated with the hyperadrenal or "shock" state; at 1 month of age, their reversal, paralleled by a rise in eosinophil count, was consistent with hypoadrenalism or the "recovery" state. These data suggested that the neonatal eosinophil pattern may have actually constituted an index of the presence of circulating adrenal corticosteroids. After 5 days

of age the infant should have recovered from the stress of a normal delivery and have excreted any excess of maternal hormones; a decrease in the infant's adrenal function, therefore, appeared to be a probable explanation for the observed increase in eosinophil count. In light of this interpretation, the subsequent fall in eosinophil count at 2 months of age obtained in a small series of infants suggested a recovery of adrenal function. This possibility of a period of relative hypoadrenalism in the infant from approximately 5 to 60 days of age might account for the clinical observation that newborn infants constitute good anesthetic and surgical risks for the first 48 hours of life, but are very poor risks for such procedures between the ages of 3 to 4 days and 1 to 2 months.

Reports in the literature dealing with elaboration of the various adrenal cortical hormones in the newborn period have emphasized the difficulty of interpreting the significance of these eosinophil patterns. Jaudon[3-5] has described a tendency for the newborn infant to develop spontaneously a deficit of desoxycorticosterone for periods varying from days to months. He demonstrated that intermediate degrees of desoxycorticosterone deficiency exist, both in severity and duration, and that glucose metabolism was apparently unaffected in these children. Several series of determinations of urinary 11-oxycorticosteroids in newborn infants have indicated, in the few children studied serially, a rise in the excretion of those substances with age.[6,7] It was difficult to reconcile the opposite implications of those findings and of the eosinophil patterns reported here. Determinations of serial urinary corticosteroid excretions on a large series of infants with concomitant eosinophil counts would help answer this discrepancy.

Detailed interpretation of the eosinophil patterns in the first week of life was even more difficult. The type a curve might have indicated an overcompensation in the recovery from birth stress, a not uncommon phenomenon in many physiologic processes. The type b curve did not lend itself to ready explanation. It was evident, however, that in the infant's first few days of life, the level of circulating eosinophils was variable and seemingly unstable; and that his eosinophil pattern after birth was much different from the recovery pattern of his mother. The mothers, moreover, exhibited a more severe reaction to the stress of birth than their offspring, the counts in four mothers showing complete absence of eosinophils. The significance of these differences must await further study of adrenal function and reaction to stress in both adults and infants.

Summary

A total of 262 eosinophil counts were done on a series of 57 infants. The mean level was 267 at birth and 483 at 1 month of age.

The eosinophil count rose significantly in the first week of life in 75% of 44 infants. Eighty-two per cent of 28 infants showed a significant rise in eosinophils from 5 to 30 days of age.

The marrow of newborn infants was relatively rich in myelocytic and rubrocytic elements and low in lymphocytes. At 30 days of age the marrow showed a significant and reciprocal change in the relative proportions of these elements.

The infant's eosinophil pattern in the first week after birth was variable and erratic. It differed quantitatively and qualitatively from that of his mother.

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SPANISH ABSTRACT

El Conteo Total de los Eosinofilos Durante el Periodo Neonatal

Un total de 262 conteos totales de los eosinofilos fueron hechos en una serie de 57 lactantes. El promedio medio de eosinifilos fue 267/cumm al nacimiento y 483/cumm al mes de nacido.

El número de eosinofilos aumentó significamente en la primera semana de vida en 75% de 44 recién nacidos. En 82% de 28 niños se demostró un aumento significante de los eosinofilos entre los cinco y treinta dias de nacidos.

La medula osea de los recién nacidos fue relativamente rica en elementos mielociticos y rubrociticos y pobre en linfocitos. A los 30 dias de nacido la medula osea demostró un cambio reciproco significante en las proporciones relativas de dichos elementos.

El conteo de los eosinofilos en la primera semana de vida es muy variable y erratico, diferenciandose qualitivamente y quantitivamente del obtenido en la madre.

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ALBUMIN THERAPY IN NEPHROSIS

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PREVIOUS experience on the treatment of nephrotic edema with high protein salt-free diet, blood transfusion, normal and concentrated human plasma and serum, amino acids, alkalinizing and acidifying salts and diets, mercurial diuretics, thyroid and other procedures has been rather disappointing. The influence of albuminuria and hypoproteinemia in the pathogenesis of nephrotic edema was not fully demonstrated. It was also found that oliguria cannot be explained on the basis of a low glomerular filtration rate, except in those cases showing glomerular involvement. Clearance and saturation tests for kidney function showed a normal or high glomerular filtration rate, increase of effective renal plasma flow and a relative and/or absolute increase of tubular reabsorptive capacity for glucose, chlorides and water in the authors' group of nephrotic children showing no symptoms of glomerulonephritis. These findings do not exclude the extrarenal influence of plasma proteins in the deposition of edema, but they indicate the participation of the kidney in its pathogenesis. An increased tubular reabsorption was stressed as a renal factor in the still obscure pathogenesis of nephrotic edema.[1]

The preparation of low-sodium concentrated human plasma albumin[2] was thought to be an ideal therapeutic procedure for replacing plasma albumin and increasing diuresis in nephrosis. Its use has given stronger information on the mechanism of albuminuria and on the important rôle played by the kidney in the excretion of edema fluid.

Luetscher,[3,4] Janeway[5,6] and others [7-11] have demonstrated that the increases of plasma volume, plasma protein concentration and diuresis are only short-lasting as most of the injected albumin is lost in the urine. A transitory increase of the glomerular filtration rate and the effective renal plasma flow was also observed in patients having the nephrotic stage of chronic glomerulonephritis.[12] Satisfactory results, however, have been occasionally reported.[13]

There seems to be a prevalent criterion that the effect of concentrated human plasma albumin (C.H.P.A.) is not the one theoretically expected in the treatment of nephrotic edema.

This paper presents as additional information clinical observations on 12 nephrotic children treated with low-sodium concentrated human plasma albumin* at the Children's Hospital of Havana. All treated children showed a typical nephrotic syndrome and were having generalized edema at the beginning of albumin therapy. Three cases showed a slight increase of urea concentration in blood, three had hematuria and in all of them

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* The product used is said to contain albumin 5 gm. and sodium salts 0.3 mg. in a 20 cc. vial, which is osmotically equivalent to 100 cc. of normal human plasma. Its intravenous injection mobilizes 70 cc. of edema fluid into the circulation within 15 min. after the termination of the injection. The recommended dose is 1 cc./lb./day (0.25 gm./lb./day) or from 12.5 to 50 gm./day according to the age of the patient.[14]

the blood pressure was normal. With the exception of one case all children were at the early stage of the nephrotic syndrome, having been ill not longer than two years at the time albumin therapy was given. None of the children had a previous history of acute hemorrhagic nephritis. Their ages varied from 2 to 9 years and there were 5 boys and 7 girls. Three control cases are included in this study; two of them received injections of hyaluronidase. In addition before and after treatment control periods were followed in some of the cases. The amount of albumin injected varied from 5 to 30 gm./day for a length of time of 8 to 57 consecutive days. The doses given to some of the patients were lower than those recommended due to the high cost of the product in this country. The observations, however, are not invalidated as they were similar to those patients receiving as much as 15 to 30 gm./day. In fact elimination of edema occurred in those children who had the lowest amount of albumin. Diuresis, proteinuria and weight were recorded daily. Proteinuria was measured by the Shevky-Stafford albuminometer and each determination was done in duplicate. Urine was diluted from 1:10 up to 1:100 with distilled water and was centrifuged at 3,000 rpm for 10 minutes. Chlorides were determined by photocolorimetry of the yellow color obtained with silver iodate. Blood chemistry was done at the beginning and end of treatment and control periods. Estimation of plasma proteins was repeatedly done also during periods of treatment. Summary of observations is given in table 1. A total of 14 courses of treatment is shown.

Results

From a total of 12 nephrotic children treated with C.H.P.A., only five seemed to respond favorably as estimated by the decrease in weight, the increase of diuresis and total or partial elimination of edema. Edema disappeared in those cases who had the lowest dose of albumin. The protein lost in the urine ranged from 25 to 100% of the amount of albumin injected. In three cases (4, 9 and 12), total proteinuria was higher than the amount injected plus the albuminuria of control period. These cases showed also a further decrease in the concentration of plasma proteins. For instance, Case 9 (J.R.M.) had around 17 gm. daily of proteinuria while receiving 10 gm. of albumin. It increased up to 33.3 gm. after 15 gm. of albumin. Case 12 (C.S.C.) showed an increase of proteinuria from 35 to 51 gm. when albumin dose was raised from 25 to 30 gm.

Total plasma protein concentration rose in only 7 instances and it decreased in 6 from a total of 14 courses of treatment. Serum albumin, on the other hand, rose in 8 and decreased in 4. An increase of serum albumin concentration was observed in all patients who had a favorable response to albumin therapy, while deposition of more edema and further gain in weight with simultaneous increase in serum albumin concentration was seen in four. The A/G ratio remained inverted in all but two cases after disappearance of edema. Normalization of concentration of plasma proteins was not accomplished in any one of the treated cases. It happened only in those cases where activity of the nephrotic syndrome had subsided regardless of the administration of albumin. Good response to treatment was seen in two girls having hematuria and increase or appearance of hematuria was seen in two cases. The diuretic effect of C.H.P.A. was evident in one case (11b).

In a comparative analysis of diuretic effect in those patients (Cases 4, 9 and 12) who had a control period study and received different doses of C.H.P.A., the following results were observed: Case 4 had a total urinary excretion of 32,740 cc. during 47 days of control period (before and after treatment) and including the oliguric effect of administration of salt (chart 1 and table 2). During 44 days of treatment he excreted only a total of

TABLE 1

ALBUMIN THERAPY IN 12 CHILDREN WITH NEPHROSIS
(Summary of 14 courses of treatment)

Name Age Sex	Albumin i. v.* gm. per day	Albumin i. v.* gm. total dose	Days of treatment	Proteinuria gm. Mx. per day	Proteinuria gm. total	Diuresis cc. Total	Wt. (kg.) ↗gain →same ↘loss	Edema†	Plasma proteins gm./100 cc. Initial and final Total	Alb.	Glob.	Urea mg./100 cc.	Cholesterol mg./100 cc.
(1) A.V.O.	5							xxx					
2 yr. ♀	10	150	15	4.3	25	2,995	↗ 0.5	xxx	3.75	1.09	2.66	53	446
									5.04	2.52	2.52	58	626
(2) S.F.	5							xxx	4.50	2.02	2.48	—	—
5 yr. ♂	10	100	15	12.4	90	2,030	→	xxx	5.81	1.49	4.32		
(3) M.Z.								xxx	4.50	1.68	2.82	56	250
2 yr. ♂	5	270	54	—	—	—	→	xxx	5.81	1.49	4.32	45	666
(4) M.N.								xxx	4.74	1.28	3.46	30	236
6 yr. ♂	5	220	44	21.4	376	18,183	↗ 3.2	xxx	4.26	1.39	2.87	72	444
(5) T.P.M.								xxx	4.57	1.73	2.84	—	—
9 yr. ♀	5	60	12	15.0	62	1,560	↘ 4.5	0	5.56	2.50	3.06	—	—
(6) O.O.G.	5							xxx	5.33	1.50	3.83	39	400
2 yr. ♀	10	240	45	12.5	30‡	12,430	↗ 0.9	xxx	3.76	1.90	1.86	30	380
(7) A.H.							↘	xx	4.79	1.83	2.96	—	330
3 yr. ♀	5	60	12	5.6	56	1,150	0.9	x	4.50	2.00	2.50	—	—
(8) O.L.							↘	xx					
5 yr. ♂	5	60	12	—	—	—	1.3	o	4.38	1.50	2.88	—	333
(9) J.R.M.	5						4.1	xxx	6.63	2.98	3.65	65	666
7 yr. ♂	15	205	24	33.3	381	5,373	↗	xxx	4.74	1.79	2.95	64	500
(10) M.M.R.							↘	xx	4.82	2.50	2.32	28	500
2 yr. ♀	5	235	47	—	—	—	1.8	o	4.70	3.00	1.70	28	231
(11a) M.C.G.							4.5	xx	5.40	1.90	3.50	35	225
3 yr. ♀	5	285	57	35.0	—	—	↗	xxx	4.20	2.00	2.20	—	980
(11b) M.C.G.							↘	xxx	3.10	1.50	1.60	—	—
3 yr. ♀	10	80	8	8.0	58.3	8,700	5.4	o	6.51	4.40	2.11	28	490
(12a) C.S.C.	5							xxx	—	—	—	—	—
3 yr. ♀	15	100	10	—	—	1,910	→	xxx	—	—	—	—	—
(12b) C.S.C.	15						0.5	xxx	6.00	3.50	2.50	42	600
3 yr. ♀	30	245	12	51.0	354.8	3,349	↗	xxx	4.60	2.40	2.20	34	700
Control Cases													
E.D.								xxx	5.56	1.34	4.22	25	500
3 yr. ♀	Hydase§	0	21	2.2	12.8	4,201	↗ 1.3	xxx	6.40	1.99	4.41	26	400
T.A.							↘	xx	5.56	1.12	4.44	43	572
3 yr. ♀	Hydase§	0	21	4.3	43.5	3,229	0.5	x	6.09	2.44	3.65	34	364
J.F.								xxx	4.74	3.58	1.16	39	460
5 yr. ♂	0	0	43	14.9	310.3	27,935	→	xxx	4.12	1.63	2.49	47	800

* Low-sodium concentrated human plasma albumin. 25/100 solution. (Cutter Lab.)
† xxx = Generalized edema and serous membrane effusion. xx = Edema of face, trunk and limb. x = Edema of face and/or ankle.
‡ Albuminuria determined the last 7 days of treatment. A total of 70 gm. of albumin i. v. in this time.
§ Hyaluronidase 150 turbidity units given per day (Wyeth Lab.).

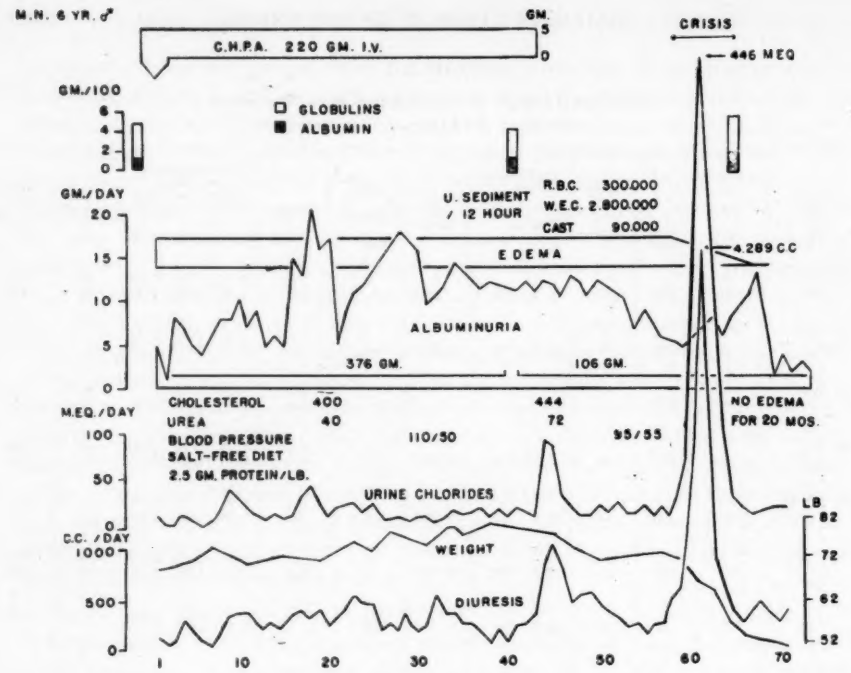

CHART 1

PROTEIN THERAPY IN NEPHROSIS

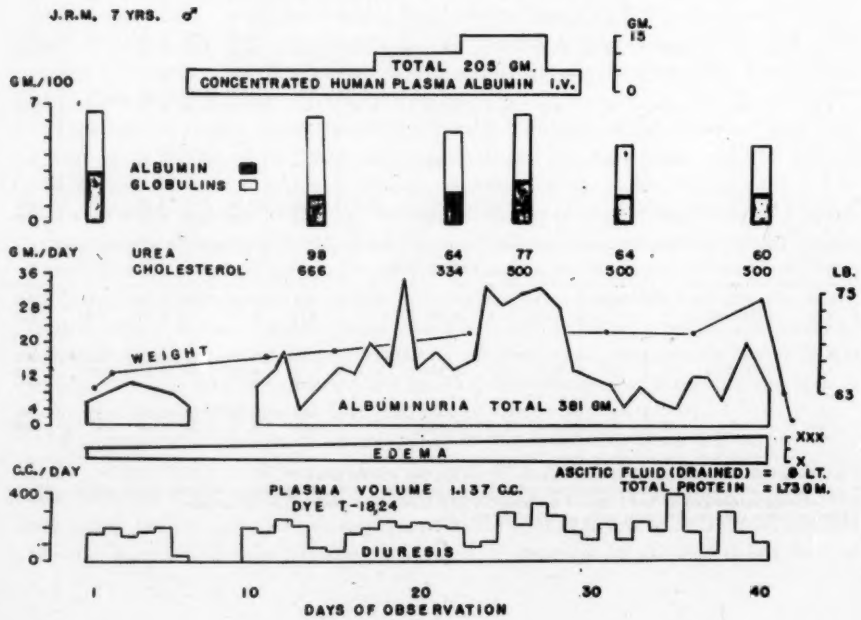

CHART 2

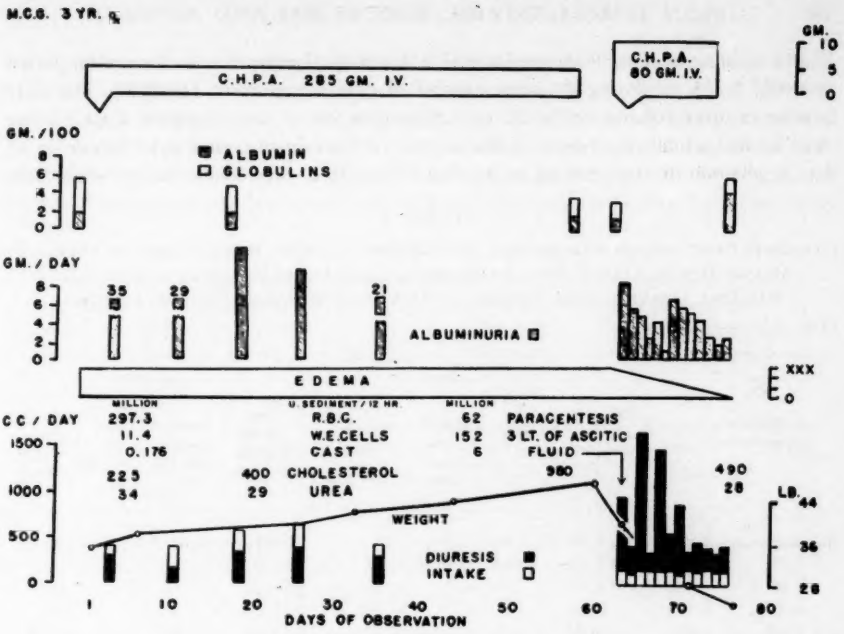

CHART 3

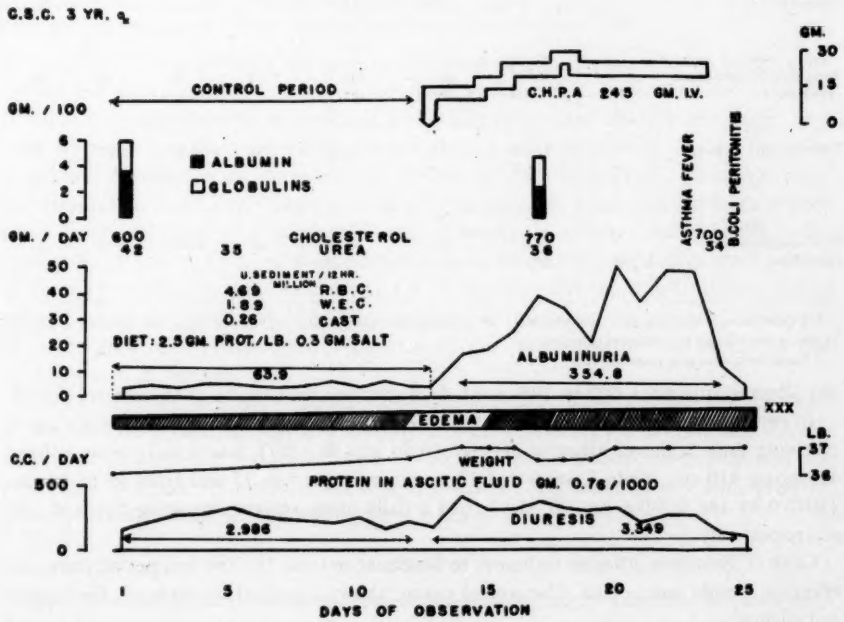

CHART 4

18,183 cc. of urine. Case 9 excreted a total of 4,129 cc. of urine in a 24 day control period and only 5,373 cc. during the same number of days of treatment (chart 2). The daily increase in urine volume was 52 cc. as compared to that of control period. Case 12 (see chart 4) had a total excretion of 2,986 cc. in a 12 day control period and 3,349 cc. in 12 days of albumin therapy, making an increase of only 30 cc./day. These cases received from

TABLE 2

CHANGES IN URINE VOLUME, ALBUMINURIA, EXCRETION OF CHLORIDES, BLOOD CHEMISTRY, EDEMA AND WEIGHT DURING 6 PERIOD STUDY IN NEPHROTIC CHILD UNDER INFLUENCE OF HIGH PROTEIN DIET, INTAKE OF SALT, ALBUMIN THERAPY AND SPONTANEOUS CRISIS OF POLYURIA

M.N. ♂ 6 yr. Case 4

Period of experiment	Days wt. edema	Urine			Blood			
		Volume total cc.	Albuminuria total gm.	Chlorides total mEq.	Total plasma protein gm./100 cc.	Serum-albumin gm./100 cc.	Globulins gm./100 cc.	Plasma chlorides mEq./l.
(1)								
High protein salt-free diet	14 61 x	7,817 (568)†	24.8 (1.8)	—	3.87	1.07	2.80	93
(2)								
Salt added to same diet. 2 gm./day	10 72 xxx	1,746 (175)	29.0 (2.9)	88.2 (8.8)	4.74	1.28	3.46	113
(3)								
C.H.P.A. 5 gm./day. Same diet	44 79 xxx	18,183 (411)	376.3 (8.6)	648.0 (14.8)	4.31	1.39	2.92	87
(4)*								
Same diet. No additional treatment.	16 58 xx	7,707 (481)	60.0 (3.7)	446.1 (27.9)	5.12	1.79	3.33	86
(5)								
Polyuric crisis. Same diet.	7 49 0	13,486 (1927)	12.7 (1.8)	1,214.3 (173.5)	5.56	1.99	3.57	85
(6)								
Final control period. Same diet.	7 49 0	2,637 (377)	32.9 (4.7)	105.3 (15.0)	5.60	2.50	3.10	85

* A small diuretic crisis was also seen in period 4. In 3 days he excreted a total of 3,254 cc. of urine and excreted a total of 11 gm. of protein and 11.2 mEq. of chlorides.

† Parenthetic data give excretion/day.

the albumin injections 600 to 700 cc. of fluid over the fluid intake of the control period.

In considering the diuretic effect of the dose of albumin given it was found that Case 4, receiving only 5 gm. of albumin per day (0.06 gm./lb./day), had a daily urine volume averaging 410 cc.; while Cases 9 and 12, receiving from 5 to 15 and from 15 to 30 gm. (0.07-0.23 and 0.4-0.8 gm./lb./day), had a daily urine volume averaging 223 and 245 cc., respectively.

Chart 3 illustrates different responses to treatment in Case 11. The first period shows no effect on weight and edema. The second period shows a gradual decrease of albuminuria and edema.

Daily changes in urine volume, albuminuria and chloride excretion were studied in Case 4 under the influence of a high protein salt-free diet, intake of salt, injection of C.H.P.A. and during spontaneous crisis of polyuria (table 2). The effect of albumin injection was not significant except for the usual increase of albuminuria. Intake of salt caused a remarkable decrease in urine and slight increase of albuminuria. In sharp contrast with these two periods of observation the spontaneous polyuric crisis was characterized by a high excretion

TABLE 3

CONSTRUCTED FROM DATA OF TABLE 2 FOR DEMONSTRATING RENAL CONTROL OF DAILY EXCRETION OF CHLORIDES AND WATER DURING PERIODS 2 TO 6 OF SAME EXPERIMENT

Period of experiment	Chlorides					Water	
	A Plasma concentration mM/l.	B Filtered (A×190)* mM/day	C Urinary excretion mM/day	D Reabsorbed (B–C) mM/day	Per cent reabsorbed D/B	E Reabsorbed 190-V l./day	Per cent of E†
(2)	113	21,470	8.8	21,461	99.9	198.8	99.9
(3)	87	16,530	15.0	16,515	99.6	189.6	99.7
(4)	86	16,340	28.0	16,312	99.8	189.5	99.7
(5)	85	16,150	173.0	15,977	98.9	188.0	98.4
(6)	85	16,150	15.0	16,135	99.8	189.6	99.7

* Glomerular filtration/day as derived from average inulin clearance/minute (132.6) in authors' nephrotic children.[1] mM/l. expressed as mM of Cl'. V: 24 hr. diuresis.

† Tubular reabsorption of water in normal children, as calculated from % (Cin-V) was found to be 96.6% due to diuretic effect of simultaneous intravenous infusion of glucose and inulin.[1] In the normal adult, according to Gamble, tubular reabsorption of water was 99.4%.[17]

of chloride and water with a simultaneous decrease of albuminuria. Plasma proteins increased but did not reach normal concentration and the A/G ratio remained inverted.

Table 3 demonstrates the renal control in the daily excretion of chloride and water. Very little difference was observed during albumin therapy with the control periods. Ingestion of salt was followed by an increase in the filtration of chloride but there was a high tubular reabsorption leading to formation of edema. On the other hand, polyuric crisis seemed to be mainly the result of a decreased tubular reabsorption of water and chlorides. A decrease from 1.5 to 10 l./day of water reabsorption was found as compared to other periods of study. This child excreted as much as 5 l. in one day. The chloride U/P ratio during polyuric crisis averaged 1.05. This also suggests an inhibition of tubular reabsorption of water since the concentration of chloride in the excreted urine was similar to that in the glomerular filtrate.

Concentration of urea and cholesterol in blood increased in two and five and decreased in four and three cases, respectively, during albumin injections. An insignificant increase of protein in the ascitic fluid was found in two patients on whom this examination was performed. No close relationship was observed between concentration of plasma proteins, albuminuria and edema in the control group of cases.

COMMENT

The experience gained from these cases was similar to that of Luetscher,[3,4] Janeway,[5,6] Routh[8] and others.[8–11] Failure of albumin therapy in nephrotic edema was due in the ma-

jority of cases to the great loss (up to 100% of albumin injected) in the urine and to the inability of kidney in excreting the edema fluid mobilized into the circulation by the osmotic effect of albumin.

In three cases total proteinuria was higher than the amount of albumin injected plus the albuminuria of control period. These patients showed also a further decrease in the concentration of plasma proteins. Dilution of plasma proteins by the mobilized edema fluid may account for the decrease in their concentration as demonstrated by Luetscher.[4] However, the inaccuracy of the method used in estimating urinary proteins may prevent detection of a loss of plasma proteins in some patients having intravenous injections of concentrated albumin, which could explain the decrease of plasma protein concentration. This fact should not be overlooked as an increase in proteinuria has been observed after ingestion of salt and in the course of intercurrent bacterial infection. By electrophoretic determination Case H.A. of Routh and collaborators[8] showed a higher proteinuria than the dose of albumin injected. An increase of proteinuria was always observed after an increase of the dose of albumin. It was impossible in these cases to obtain a positive balance by gradually increasing the dose of albumin. The response to albumin therapy was irregular and inconsistent. Decrease in weight and edema was seen in patients retaining part of the protein injected (chart 3) and in others losing as much as 100% in the urine. Conversely, increase of weight and edema with simultaneous increase in the concentration of plasma albumin was seen in four cases. The great urinary leakage of protein was similar in both the nephrotic syndrome with and without clinical manifestations of glomerular involvement. Disappearance of edema was seen in two girls having hematuria. The relationship observed between the dose of albumin injected and the increase in proteinuria provides valuable information in favor of an abnormal permeability of the glomerular capillary. It also excludes both the possibility of an abnormal production of plasma proteins and of a decreased tubular reabsorption of the normal small amount of protein filtered[15] as the primary causes of albuminuria in nephrosis. Leakage of protein through the peripheral capillary system was not observed. The lack of diuretic response in patients retaining part of the albumin injected was another significant fact. Since expansion of plasma volume, increase of the effective renal plasma flow and glomerular filtration rate have been shown to occur after intravenous administration of albumin, failure of diuresis could be in part dependent on the functional condition of tubular epithelium. The data in table 3, the previous finding of an increased tubular reabsorption[1] and the presence of an antidiuretic substance in the urine of edematous nephrotic patients[16] are consistent with this clinical observation. The final word on these controversial observations in nephrosis cannot be said until urinary leakage of injected protein can be prevented by some additional therapy.

The increase of urea concentration in the blood of some of these patients was not the result of albumin therapy. It was related to the functional condition of kidneys and the oral intake of protein. Under certain conditions (such as urea retention and anorexia) and during short periods of treatment, it was found that albumin therapy replaced high protein diet without further retention of urea and other substances derived from the digestion and metabolism of dietary protein. It was possible to approach the same effect (i.e., decrease in urea concentration) with a low or a free protein diet and small intravenous doses of concentrated human albumin.

SUMMARY

Twelve nephrotic children were treated with intravenous injections of low-sodium con-

centrated human plasma albumin. Favorable response, as judged by the decrease in weight and edema and the increase in diuresis, was only seen in five cases.

Lack of therapeutic effect on nephrotic edema was due in the majority of cases to the great urinary loss of injected albumin and to the inability of the kidney to excrete the edema fluid mobilized into the circulation by the osmotic effect of albumin.

Addendum

Since this paper was submitted for publication, three more patients with the nephrotic syndrome have been injected with low-sodium concentrated human plasma albumin.

Case A. A 15 year old boy received a total of 1,030 gm. of C.H.P.A. (0.17 to 0.39 gm./lb./day) in 40 days. Total diuresis was 14.645 cc. (366 cc./day) and total albuminuria was 1,438 gm. (35.9 gm./day). Concentration of total plasma proteins decreased from 4.1 to 3.9 gm./100 cc. In a 10 day control period his diuresis was 2,722 cc. (272 cc./day) and total albuminuria was 145.6 gm. (14.56 gm./day). Total plasma proteins increased up to 4.8 gm./100 cc. and serum-albumin concentration remained the same There was no practical effect on his weight and edema. Daily diuresis during albumin injections was actually only 288 cc. after discounting from total diuresis the amount of 3,090 cc. of the fluid given with the albumin. In other words, increase of diuresis over the control period was only 16 cc./day.

Case B. A 2 year old boy had a total of 180 gm. of albumin injected over a period of 6 days (30 gm./day or 1.25 gm./lb./day). Diuresis was 1,825 cc. and total albuminuria was only 85 gm. There was no effect on his edema. Despite the fact that 50% of the injected albumin was not lost in his urine, a diuretic response was not observed.

Case C. A 15 year old girl showed a spontaneous diuresis while receiving a total of only 95 gm. of C.H.P.A. in 19 days (0.06 gm./lb./day). Her diuresis was 23,850 cc. and total proteinuria was only 93.5 gm. In an 11 day control period her diuresis was 20.980 cc. and total proteinuria was 153.9 gm. Even though albuminuria during control period was higher than during albumin therapy, she remained free from edema and her plasma proteins increased up to 5.8 gm./100 cc. with a 1.6 A/G ratio.

None of these three patients had gross hematuria or elevated blood pressure and they were also at the early stage of the nephrotic syndrome. The two first cases, however, showed 65 and 99 mg./100 cc. of urea in blood which returned to normal concentration while on a protein-free diet.

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SPANISH ABSTRACT

Albuminoterapia en la Nefrosis

Se trataron doce niños nefrósicos con inyecciones endovenosas de albúmina de plasma humano pobre en sodio (solución al 25 por ciento). Solamente cinco casos respondieron favorablemente con disminución del peso y del edema y aumento de la diuresis.

La falta de efecto terapéutico en los restantes casos se debió a la gran pérdida urinaria de la albúmina inyectada y a la incapacidad del riñón para excretar el líquido de edema movilizado hacia la circulación por el efecto osmótico de la albúmina.

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STUDIES OF ACID BASE EQUILIBRIUM IN PREMATURE INFANTS

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IT HAS been fairly well established that well premature infants exist in a state of acidosis.[1-5] However, there have been no studies on a large group of premature infants in which an analysis was made of (1) the range of chemical variations that may occur in normal, well, premature infants, or (2) the relationship of the carbon dioxide content and pH to other fractions of the acid base balance, and (3) the correlation of such findings with the clinical status of the infants. Therefore, this study of the variations in the chemical physiology of premature infants was made.

METHOD OF STUDY

Ninety-one analyses for pH, total CO_2 content, with calculated pCO_2 of arterial blood were made on 64 premature infants, aged 1 to 65 days, and weight 1.1 kg. to 2.3 kg. The acid base analyses were completed on 60 premature infants, on 73 different occasions. Insofar as possible the infants were studied during their first week of life, and determinations were made again on the same babies at weekly intervals in an effort to correlate their age with a possible change in chemical values. The control group was comprised of 16 healthy adolescent males between 10 and 14 yr. of age.

A technic for sampling true arterial blood in premature infants was developed for this study. Only blood from the temporal artery was used in the acid base studies for the following reasons: (1) The arterial blood is a better reflection of the chemical changes in the vascular system than venous blood, since the latter may reflect changes only in a local vascular area of the body. (2) The correlation of acid base balance studies with plasma oxygen studies (to be reported) demanded the use of arterial blood as well as venous blood. (3) The correlation of alveolar carbon dioxide tension with acid base studies could only be obtained by calculation of the carbon dioxide tension of arterial blood in premature infants.

Sampling Technic.—A 5 ml. syringe was filled with 5 ml. of heparin (40 mg./100 ml. solution) and dried in vacuo. A drop of heparin solution was placed on the tip of the plunger which was also dried in vacuo. The plunger of the syringe was coated with light mineral oil (USP) and inserted into the barrel of the syringe. A sharp 22 gauge, 1 inch, long bevel needle was attached and sealed to the tip of the syringe by collodion. The temporal artery was palpated and observed for pulsations about 0.5 cm. anterior to the upper anterior attachment of the external ear. The artery usually has visible pulsation for a distance of 1 to 2 cm. in this area. Arterio puncture was done and 3 ml. of blood was withdrawn into the syringe after which any small bubble of trapped air was expelled. The needle was then replaced with a serum bottle rubber cap, and the syringe was rotated to insure mixing with the anticoagulant. One ml. of blood was removed from either the external jugular vein or the temporal vein by the same technic. The syringes were then packed in ice.

Three ml. of blood were removed from the femoral artery and 2 ml. of blood were removed from the antecubital vein of the control subjects and subjected to the same conditions just listed.

Chemistry Methods.—The samples were kept at 0°C. until the analyses were performed. That portion to be used for the plasma determinations was transferred under light mineral oil to Pyrex tubes, and after centrifugation was kept at 0°C. Analyses were usually done in duplicate.

Blood pH was determined using the Cambridge Electron-Ray pH Meter (Research Model). The meter was kept in an incubator (Liedberg Anhydric Incubator) which was maintained at a tempera-

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ture of 38°C. All determinations were performed at this temperature. The blood sample was injected directly from the sampling syringe into the micro condenser-type glass electrode. Ten minutes were allowed for temperature equilibration before readings were taken. The meter was calibrated before each sample and checked again afterwards with pH standard solution prepared from Coleman buffer tablets (7.40 pH ± 0.02 at 30°C.).[6]

Total plasma CO_2 content was determined on 0.2 ml. of plasma by the manometric method of Van Slyke and Neill.[7]

Plasma chloride was determined by the iodometric titration procedure of Van Slyke and Miller.[8] Because the amount of plasma available was extremely limited, only 0.04 ml. of plasma was analyzed. Duplicates were always run and whenever the amount of plasma was ample triplicate analyses were run. In order to insure correction for deviations in the volumes of the pipettes and as a further check on the reagents, a 100 mEq./l. chloride standard was simultaneously treated exactly as an unknown. 0.1 N HCl prepared from constant boiling HCl according to Hulett and Bonner[9] was used as the standard. The same 0.1 N HCl was used for the titration in the total base. The calculation then became:

$$\frac{\text{ml. 0.01151 N thiosulfate used for the unknown}}{\text{ml. 0.01151 N thiosulfate used for the standard}} \times 100 = \text{mEq. chloride/l. of plasma.}$$

Plasma protein was determined on approximately 0.02 ml. of plasma by the gradient tube method of Lowry and Hunter.[10] The standards used were the copper sulfate standards of Phillips, Van Slyke et al.[11]

Plasma inorganic phosphate was determined by a micromodification of the procedure of Fiske and Subbarow,[12] using 0.1 ml. of plasma.

Total base was done by the electrodialysis procedure of Keys[13] as modified by Sobel, Rockenmacher and Kramer.[14] 0.1 ml. of plasma was analyzed and the trapped base in the cathode tube was titrated with 0.1 N HCl (see chloride above), using a Rehburg micro-burette.

Calculations.—The CO^2 tension was calculated by the Lyon chart for graphic calculation of serum or plasma values by the CO_2 solubility equation and the Henderson-Hasselbalch equation.[15]

"R" represents the acid constituents of the blood not analyzed in the study and includes sulfate, organic acids and phosphate (in those infants in which phosphate was not analyzed). "R" was calculated by subtracting the sum of the acid fractions from the total base of the blood. Plasma phosphate was determined in 13 infants and 13 adults.

Statistics.—All statistical analyses and correlations were done by the Statistical Research Laboratory, University of Michigan.

Clinical History

TABLE 1

Sex and Race of 64 Premature Infants

	No.
Sex	
Boys	33
Girls	31
Total	64
Race	
Negro	39
White	25
Total	64

Subjects.—Sixty-four infants, aged 1 to 65 days, and 1.1 kg. to 2.3 kg. in weight were studied in three hospitals.* Table 1 reveals that the premature infants were about equally divided in respect to sex, but there were more Negro than white infants in this study.

The known causes of prematurity as listed in table 2 are reliable for this group, but

* The 3 hospitals were The Children's Hospital of Michigan, Detroit, Herman Kiefer Hospital, Detroit, and University of Michigan Hospital, Ann Arbor, Mich.

since complete prenatal history was not available in many infants due to factors beyond hospital control, the "unknown causes" are large (61%). Table 2 reveals that 51 infants had no difficulty in initiating or maintaining respiration at birth, and were considered to be in good condition. Thirteen of the 64 infants at birth had difficulty in initiating and maintaining respiration, or had a poor cry and/or periods of cyanosis. Of these 13 infants,

TABLE 2

PRENATAL AND BIRTH HISTORY OF 64 PREMATURE INFANTS

Causes of Prematurity		No.	Pts.	% Pts.
Maternal Complications			12	18.7
Toxemia		2		
Lues		2		
Hypertension (cesarean)		1		
Heart disease (mitral stenosis)		1		
Antepartum hemorrhage		1		
Anemia		1		
Malnutrition		1		
Trauma (fall)		1		
Premature rupture of membranes		2		
Multiple Births				18.7
Twins	8 sets	11		
Triplets	1 set	1		
	9	12		
Congenital anomalies		1		1.5
Unknown				61.1
Birth History				
Duration of Labor	Range 1–24 hr. Average 9 hr.			
Type of Birth				
Vertex		38		59.4
Breech		10		15.6
Unknown (unattended)		12		18.7
Precipitate		3		4.8
Cesarean		1		1.5
Condition at birth				
Poor—Fair		13		20
Good		51		80

nine were improved in 48 hours and had no further difficulty. Three infants had marked clinical respiratory distress which persisted in the neonatal period. Two of these, O'D and Pa, had irregular rapid respirations and cyanosis if taken out of oxygen for 24 and 45 days, respectively. The third one, infant Fi, had an irregular respiration with noisy breathing which was due to a congenital nasal defect. One infant, Sm, who was cyanotic at birth and had difficulty maintaining respirations, died within 36 hours. (See Hospital Course.)

Feeding.—All the premature infants in table 3 marked CHM hospital had a Dryco for-

mula with added carbohydrate which was started as a 10 cal./oz. mixture the second day of life and gradually increased to 20 cal./oz., 45 cal./lb. by the end of one week. Vitamin C 50 mg. was started on the seventh day, vipenta® minims 10 (vitamin A 5000 USP, vitamin D 1000 USP, ascorbic acid 50 mg., thiamine 1 mg., riboflavin 1 mg., niacinamide 2 mg.), and drisdol® 2000 USP units on the tenth day of life.

All the premature infants marked HK in table 3 had an evaporated milk formula with added carbohydrate (dextri-maltose) and a caloric intake similar to premature infants from CHM hospital. HK babies received no vitamins while the study was in progress.

Newborn Care.—All babies under 1.8 kg. in weight and any babies over 1.8 kg. who were in respiratory distress or who were ill on admission to the ward were routinely given oxygen therapy (concentration of 45 vol. %) at CHM hospital. No babies at HK received oxygen therapy unless they had respiratory distress which was very infrequent. All babies were placed in incubators or heated cribs depending upon their birth weight and general condition.

Hospital Course.—The majority (87%) of the premature infants were considered to be healthy, and 13% were considered to be moderately ill in some manner. The division into sick and well groups was based entirely on a clinical evaluation of infection at or near the time of sampling. Since the difference between clinically well and sick premature infants is so hard to define unless the illness is severe, there is no absolute method of objective evaluation. It needs emphasis that no premature infants with severe diarrhea or severe dehydration were included in this study. In the group of eight sick premature infants, three had omphalitis, two had onset of loose stools, one had thrush, one impetigo, and one had impetigo and conjunctivitis.

Two of the 64 premature infants died. One baby, At, in the aforementioned sick group, died seven days after blood was drawn for chemical analysis. An autopsy* diagnosis of healing omphalitis, B. coli sepsis, diarrhea, dehydration, pulmonary hemorrhage, kernicterus was made. The other baby, Sm, one of twins, product of a 78 hour labor, had cyanosis and respiratory difficulty at birth, and died about 36 hours of age. Blood for analysis was taken 10 hours prior to death. Autopsy* revealed no specific cause of death other than that which can be ascribed to the general state of prematurity.

Three patients had evidence of clinical edema. In one infant the edema lasted until 19 days of age. In the second infant the edema lasted until 4 days of age and the third infant with edema was one of the two just reported autopsies (Sm). It is interesting that the authors have not noted the marked manifestations of edema as indicated by Smith,[16] although subclinical edema, a matter wholly of arbitrary definition, is probably present in most newborn, small premature infants.

Results

The study revealed that the majority of premature infants had a slight uncompensated metabolic acidosis. No premature infant in the study showed all fractions of the acid base components within the adult normal range. However, if plasma protein which was consistently low and inorganic phosphate which was consistently high be excluded, one of the 73 infants had chemical determinations which approached the normal adult range. This one infant is appropriately indicated in table 3 which lists the individual chemical data on all the premature infants and control subjects.

* Autopsies done by Dr. R. Mudgett in Dr. W. Zuelzer's department of The Children's Hospital of Michigan, Detroit.

TABLE 3

ACID BASE EQUILIBRIUM ON HEALTHY PREMATURE INFANTS

Name	Sex	Color	Hosp.	Gestation period mo.	Birth length cm.	Birth wt. kg.	Age days	Present wt. kg.	pH	Total CO_2 content mEq./l.	Free CO_2 content* mEq./l.	Bound CO_2 content mEq./l.	Cl. mEq./l.	Prot. (gm.%)	Prot. base-binding power mEq./l.	Inorganic P mEq./l.	Total base mEq./l.	"R" mEq./l.	CO_2 Tension (calculated) mm.Hg
1An	F	C	CHM	? Term	45	1.4	35	2.1	7.37	21.6	1.1	20.5	116.0	4.78	11.6		163.0	15.0	36.5
2Wh	F	C	UM		44	1.8	22	2.2	7.36	19.2	1.0	18.2	116.0	5.47	13.3		157.0	10.0	33.0
3Wh2							22	1.9	7.29	16.5									33.0
4Ba	M	C	HK	8		2.4	2	2.3	7.23	18.1	1.3	16.8	117.0	5.29	12.9		161.0	14.0	41.0
5Bi	F	W	HK	8	46	2.0	5	2.3	7.21	20.6	1.5	19.1	114.0	5.12	12.4		160.0	15.0	49.0
6Br	M	W	CHM	7	35	1.1	29	1.3	7.27	20.7	1.3	19.4	110.0	5.43	13.3		158.0	15.0	43.0
7Bu							5	1.1	7.33	18.4									34.0
7bBu							15		7.23	19.2									44.0
7cBu	F	C	CHM	8½	36	1.3	20	1.4	7.23	17.2	1.2	16.0	119.0	5.47	13.3		154.0	6.0	39.0
8Bu							6	1.0	7.20	17.5									42.0
9Ca	M	C	CHM		35	1.1	10	1.2	7.18	18.3	1.4	16.9	107.0	5.43	13.3		152.0	15.0	46.0
9bCal							17	1.3	7.31	24.4									46.5
10Ca	M	C	HK	8	40	1.5	3	1.5	7.31	14.4	0.8	13.6	117.0	4.78	11.6		161.0	19.0	27.5
11Ci	M	W	CHM	8	36	1.1	35	1.7	7.31	20.8	1.2	19.6	110.0	5.12	12.4		161.0	19.0	39.5
†12Co	F	W	CHM	7–8	35	1.3	21	1.4	7.37	22.1	1.1	21.0	108.0	5.12	12.4		156.0	15.0	37.0
12bCo							28	1.6	7.38	23.4									38.5
13Co	M	W	HK	7	35	1.2	3	1.1	7.31	21.7	1.3	20.4	116.0	5.29	12.9		159.0	10.0	41.5
13bCo	M	W	HK	7	35	1.2	16	1.4	7.29	18.7	1.1	17.6	119.0	4.45	10.0		153.0	6.0	37.5
13cCo	M	W	HK	7	35	1.2	30	1.9	7.41	21.7	1.0	20.7	108.0	4.45	10.8		159.0	20.0	33.5
14Co	M	W	HK	7	38	1.2	3	1.2	7.26	21.1	1.4	19.7	106.0	4.78	11.6		158.0	21.0	45.0
14bCo	M	W	HK	7	38	1.2	30	1.8	7.44	25.6	1.1	24.5	111.0	4.10	10.0		156.0	10.0	37.0
15Da	M	C	HK	Term	43	2.0	5	2.2	7.36	20.1	1.0	19.1	120.0	5.47	13.3		163.0	11.0	34.5
16bFi							12	1.5	7.22	22.0									51.0
17Fi	M	C	CHM	? Term	43	1.8	1	1.8	7.27	20.4	1.3	19.1	114.0	5.12	12.4		170.0	25.0	42.0
18Ge							2	1.3	7.40	22.5									36.0
19Gi	F	C	HK		42	1.7	7	2.0	7.36	15.5	0.8	13.7	114.0	5.12	12.2		154.0	14.0	26.5
20Ha	F	C	HK	7	39	1.3	2	1.3	7.32	22.2	1.3	20.9	106.0	5.47	13.3		161.0	21.0	42.0
20bHa							15	1.5	7.46	19.4									27.0
21Ja	F	C	CHM	7		1.9	5	1.8	7.25	15.5	1.0	14.1	115.0	5.12	12.4		156.0	15.0	33.0
22Ma1							2	1.7	7.40	23.0									36.0
23Ma	M	W	HK	? Term	43	1.7	6	1.7	7.40	20.3	1.0	19.3	115.0	4.78	11.6		158.0	12.0	32.0
24Ma	M	C	CHM		43	2.0	36	2.0	7.30	10.9	0.7	10.2	113.0	5.47	13.3		153.0	23.0	21.5
25Mc	F	C	CHM	8½	45	2.0	2	1.9	7.36	18.7	1.0	17.7	108.0	5.47	13.3		155.0	16.0	32.0
26Mo	M	W	CHM	7½	44	1.8	8	1.8	7.36	23.5	1.2	22.3	107.0	5.12	12.4		157.0	15.0	40.5
26bMo							17	2.1	7.40	24.9									39.0
27Pa	M	C	CHM	7½	36	1.1	40	1.5	7.26	25.6	1.7	23.9	101.0	5.47	13.3		154.0	16.0	52.5
28Sa	F	C	CHM	7	38	1.3	18	1.4	7.27	14.6	0.9	13.7	114.0	5.81	14.1		154.0	12.0	30.5
28bSa							25		7.25	20.4									44.0

* For the calculation of free carbon dioxide with Henderson-Hasselbalch equation, the value used for bicarbonate concentration is assumed to be the difference between the free and total carbon dioxide without correcting for small amount of carbamate.

† Almost normal acid-base.

TABLE 3—(*continued*)

Name	Sex	Color	Hosp.	Gestation period mo.	Birth length cm.	Birth wt. kg.	Age days	Present wt. kg.	pH	Total CO_2 content mEq./l.	Free CO_2 content* mEq./l.	Bound CO_2 content mEq./l.	Cl. mEq./l.	Prot. (gm.%)	Prot. base-binding power mEq./l.	Inorganic P mEq./l.	Total base mEq./l.	"R" mEq./l.	CO_2 Tension (calculated) mm.Hg
28cSa	F	C	CHM	7	38	1.3	33	1.7	7.24	22.3	1.5	20.8	114.0	4.78	11.6		158.0	12.0	50.0
29Sc	F	W	CHM		40	1.7	28	1.9	7.24	23.7	1.6	22.1	103.0	5.47	13.3		156.0	18.0	53.0
29bSc	F	W	CHM		40	1.7	35	2.0	7.40	18.0	0.9	17.1	111.0	6.15	14.9		156.0	13.0	28.5
30Se	M	C	CHM	6½	35	1.3	2	1.1	7.26	19.5	1.3	18.2	107.0	5.64	13.8		159.0	20.0	41.5
31Sh	M	C	CHM	6½	42	1.5	7	1.3	7.19	16.4	1.2	15.2	110.0	5.47	13.3		160.0	22.0	40.0
32Sm	F	C	HK	8½	43	1.5	3	1.6	7.26	14.7	0.9	13.8	112.0	5.47	13.3		159.0	20.0	31.5
33Th	F	C	HK	8	42	1.4	3	1.4	7.38	25.0	1.3	23.7	114.0	4.95	12.0		166.0	16.0	41.0
34Wa							1	1.5	7.37	21.0									35.0
34bWa	F	W	CHM	8	41	1.6	11	1.7	7.28	21.4	1.3	20.1	110.0	5.47	13.3		160.0	17.0	43.5
†34cWa	F	W	CHM	8	41	1.6	16	1.7	7.37	25.6	1.3	24.3	108.0	5.47	13.3		157.0	11.0	43.0
35We	F	C	HK			1.5	4	1.5	7.25	17.3	1.1	16.2	120.0	5.81	14.1		168.0	12.0	37.5
36Wi	F	C	HK	8	39	1.4	3	1.4	7.29	18.8	1.1	17.7	109.0	4.10	10.0		159.0	22.0	38.0
52Ca	M	C	CHM		41	1.7	16	1.7	7.37	19.4	1.0	18.4	112.0	5.47	13.3		162.0	18.0	33.0
54Dan							14	1.9	7.29	19.8									39.5
56Jo	F	C	CHM		43	2.0	5	1.8	7.34	18.5	1.0	17.5	114.0	5.12	12.4		157.0	13.0	33.0
56bJo							19	3.4	7.27	15.0									31.0
57Me	M	W	CHM		38	1.5	9	1.5	7.34	21.1	1.1	20.0	109.0	5.81	14.1		160.0	17.0	37.5
57bMe							26	2.0	7.29	24.4									49.0
57cMe	M	W	CHM		38	1.5	33	2.3	7.24	22.3	1.5	20.8	117.0	5.12	12.4		164.0	14.0	50.0
58Re	M	C	CHM		45	2.0	11	1.8	7.23	12.7	0.9	11.8	105.0	5.81	14.1		153.0	22.0	29.0
58bRe							19	1.5	7.29	14.8									29.5
59Va	M	W	CHM	7	41	1.8	14	1.8	7.48	19.9	0.8	19.1	99.0	5.43	13.2		155.0	24.0	26.5
59bVa	M	W	CHM	7	41	1.8	25	2.1	7.34	19.1	1.0	18.1	112.0	4.78	11.6		162.0	14.0	34.0
60Wa	M	C	CHM		40	1.7	6	1.3	7.34	22.7	1.2	21.5	115.0	4.95	12.0		159.0	11.0	40.5
16Fi	M	C	CHM	8	39	1.5	4	1.4	7.35	22.3	1.2	21.1	112.0	5.12	12.4		156.0	11.0	39.0
62Od	F	W	CHM	8	38	1.1	44	1.7	7.41	29.1	1.4	27.7	103.0	4.78	11.6		161.0	19.0	44.5
62bOd							57	2.0	7.37	24.2									44.5
62cOd	F	W	CHM	8	38	1.1	65	2.3	7.36	22.9	1.2	21.7	111.0	4.78	11.6		164.0	20.0	39.0
63Sm	M	W	CHM	8½	38	1.3	2	1.2	7.21	18.7	1.4	17.3	111.0	5.12	12.4		166.0	25.0	44.0
37Ca	F	W	HK	8	47	1.9	6	2.0	7.25	25.4	1.6	23.8	99.0	4.95	12.1	4.8	155.0	15.0	52.0
38Da	F	C	CHM	8	42	1.9	12	1.9	7.26	17.9	1.2	16.7	120.0	6.15	15.0	3.8	171.0	16.0	38.0
39Da	M	W	HK	8		1.8	6	1.9	7.31	13.1	1.1	17.0	111.0	5.81	14.1	4.4	157.0	11.0	34.5
40Em	M	C	CHM		40	1.5	19	1.6	7.34	21.3	1.1	20.2	106.0	5.81	14.1	4.3	155.0	10.0	38.0
41Fr	F	C	HK		43	1.6	14	1.8	7.31	20.7	1.2	19.5	112.0	5.29	13.0	4.1	158.0	9.0	39.0
42Hu	F	C	CHM	7½	39	1.4	5	1.3	7.33	23.1	1.3	21.8	115.0	5.81	14.1	4.0	162.0	7.0	42.0
43Lo	F	C	CHM	8		1.2	22	1.4	7.35	24.5	1.3	23.2	106.0	5.12	12.4	4.4	158.0	12.0	43.0
44Mc	M	C	CHM		48	2.0	5	1.9	7.32	22.4	1.1	21.3	112.0	5.47	13.3	3.7	157.0	7.0	26.5
45Mc	F	C	HK		40	1.8	7	1.9	7.23	15.7	1.1	14.6	118.0	5.12	12.4	4.5	158.0	9.0	35.5
46Ma	M	W	HK	Term	48	2.1	1	2.1	7.34	23.6	1.3	22.3	110.0	6.51	15.7	3.7	157.0	5.0	42.0
47Ow	F	C	CHM		35	1.1	10	1.3	7.27	17.3	1.1	16.2	110.0	5.12	12.4	4.4	165.0	22.0	36.0
65Th	M	W	HK		42	1.6	19	2.1	7.32	21.3	1.2	20.1	110.0	4.27	10.4	3.8	156.0	12.0	40.0
48Wy	F	W	CHM	8¼	41	1.6	12	1.7	7.28	19.8	1.2	18.6	111.0	4.78	11.6	3.8	158.0	13.0	40.5

TABLE 4

ACID BASE BALANCE OF SICK PREMATURE INFANTS

Name	Sex	Color	Hosp.	Gestation period mo.	Birth length cm.	Birth wt. kg.	Age days	Present wt. kg.	pH	Total CO_2 content mEq./l.	Free CO_2 content mEq./l.	Bound CO_2 content mEq./l.	Cl. mEq./l.	Prot. (gm.%)	Prot. base-binding power mEq./l.	Total base mEq./l.	"R" mEq./l.	CO_2 tension (calculated) mm.Hg
49At	F	C	CHM	7	36	1.4	4	1.4	7.28	17.8	1.1	16.7	117.0	5.12	12.4	163.0	17.0	36.5
50Be	M	W	UM	6	38	1.3	5	1.3	7.34	19.2	1.1	18.1	105.0	5.47	13.3	155.0	19.0	34.5
50bBe	M	W	UM	6	38	1.3	15	1.4	7.31	21.4	1.2	20.2	107.0	5.29	12.8	157.0	17.0	40.5
51Ca	M	C	CHM		41	1.7	7	1.5	7.19	12.0	0.9	11.1	124.0	6.16	15.0	160.0	10.0	29.5
53Ci	M	W	CHM	8	35	1.0	35	1.5	7.27	19.6	1.2	18.4	115.0	4.78	11.6	160.0	15.0	41.0
53bCi	M	W	CHM	8	35	1.0	43	1.7	7.32	22.8	1.3	21.5	116.0	4.78	11.6	159.0	9.0	43.0
53cCi	M	W	CHM	8	35	1.0	56	1.9	7.29	20.6	1.3	19.3	109.0	4.45	10.9	166.0	27.0	41.0
54Da	F	C	CHM		40	1.9	5	1.9	7.33	20.7	1.2	19.5	104.0	5.47	13.3	156.0	19.0	38.0
55Do	F	W	CHM	7	40	1.3	5	1.2	7.26	21.2	1.4	19.8	115.0	4.45	10.9	165.0	19.0	45.0
61Wh	M	W	CHM	7	45	1.9	16	1.9	7.31	19.7	1.1	18.6	111.0	5.47	13.3	158.0	11.0	37.5
64Wr	M	W	CHM	7½	42	1.9	8	1.7	7.42	19.9	1.0	18.9	111.0	5.64	13.7	166.0	22.0	30.0

TABLE 5

ACID BASE BALANCE IN YOUNG ADULT CONTROLS (10–14 YEARS OF AGE); FEMORAL ARTERY BLOOD PLASMA AND ANTECUBITAL VEIN PLASMA

Name	pH		Total CO_2 content mEq./l.		Free CO_2 content mEq./l.		Bound CO_2 content mEq./l.		Calculated pCO2 mm.Hg		Cl. mEq./l.		Protein base binding		Total base mEq./l.		"R" mEq./l.		Capillary blood plasma PO4 mEq./l.
	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	Art.	Ven.	
Brd	7.38	7.33	24.0	27.3	1.2	1.5	22.8	25.8	39.5	50.0	105		17.4		155		9		2.58
Brn	7.40		23.3	27.4	1.1		22.2		37.0		102	103	17.4	17.4	154	154	11	6.0	2.08
Ne	7.41	7.36	23.1	25.0	1.1	1.3	22.0	23.7	35.5	43.0	104	105	15.7	15.7	155		12		1.77
Wa	7.42	7.40	24.9	25.9	1.1	1.2	23.8	24.7	37.5	41.0	98	99	17.4	17.4	156		16		1.81
Tr	7.41	7.37	25.1	26.4	1.2	1.3	23.9	25.1	38.5	44.5	103	103	16.6	16.6	153	155	8	9.0	1.98
Fe	7.40	7.35	26.1	27.3	1.3	1.4	24.8	25.9	41.0	48.0	102	103	17.4	17.4	155	158	9	10	1.92
Ba	7.44	7.42	24.3	25.5	1.1	1.2	23.2	24.3	35.0	38.5	102	100	17.4	17.4	152	152	8	9	1.87
Go	7.44	7.36	24.4	28.9	1.1	1.5	23.3	27.4	35.0	49.0	103	98	17.4	17.4	152	154	7	10	2.08
Ga	7.42	7.35	24.2	24.0	1.1	1.3	23.1	22.7	36.5	42.0	99	100	16.6	16.6	154	154	14	13	1.83
Pa	7.41	7.32	23.3	25.3	1.1	1.4	22.2	23.4	36.0	47.5	101	99	16.6	16.6	155	154	14	13	1.98
Mo	7.39	7.37	26.4	29.6	1.3	1.5	25.1	28.1	42.5	49.5	100	101	17.4	17.4	153	159	9	11	2.03
Ko	7.44	7.38	24.2	28.6	1.1	1.4	23.1	27.2	35.0	47.0	101	101	17.4	17.4	153	157	10	10	2.08
Gr	7.41	7.36	24.5	26.8	1.1	1.4	23.4	25.4	37.5	46.0	102	102	16.6	16.6	154	153	11	8	2.03
Ma*	7.44	7.32	22.1	27.6	1.0	1.6	21.1	26.0	32.0	52.0	104	100	17.4	17.4	154	155	10	10	
Cl*	7.43	7.34	21.4	23.8	1.0	1.3	20.4	22.5	31.5	42.5	107	102	17.4	17.4	158	157	12	14	
Th*	7.44	7.40	22.0	26.7	1.0	1.3	21.0	25.4	32.0	42.0	106	105	16.6	16.6	156	155	11	7	

* Hyperventilated while taking blood specimen.

TABLE 6

ACID BASE EQUILIBRIUM OF PREMATURE INFANTS AND ADULT CONTROLS—ARTERIAL BLOOD

	No. of pts.	No. of det'ns.	pH ±0.02	CO_2 content mEq./l. ±0.5	pCO_2 mm.Hg	Cl. mEq./l. ±1.2	Prot. base bind mEq./l. ±0.5	PO^4 mEq./l. ±0.03	Total base mEq./l. ±1.0	R mEq./l.
Premature Infants										
Well	52	62	Av. 7.31	20.2	39.0	111.0	12.7		159	15
								4.1 (13)*		11
Sick	8	11	Av. 7.30	19.5	38.0	112.0	12.6		161	17
Total	60	73	Av. 7.31	20.1	38.0	111.0	12.7		159	15
								4.1		
Adult Controls										
Well	13	13	Av. 7.41	24.4	37.4	102.0	17.0		154	11
								2.01*		
Adult										
Range of		13	7.38	23.1	35.0	98.0	15.7		152	7
Values			7.44	26.4	42.5	105.0	17.4		156	16
Premature Infants										
Range of		73	7.18	10.9	21.5	99.0	10.0	3.7	152	
Values			7.48	29.1	58.0	124.0	15.7	4.8	171	

* Adult inorganic phosphates of plasma calculated on pH 7.40.

Table 6 is a summary of the data of tables 3, 4 and 5 and compares the averages and ranges of 73 values for 60 well and sick premature infants to 13 individuals in the control group. Three of the 16 individuals in the control group were eliminated in these values, because of hyperventilation. The average values for pH, total CO_2 content and protein were reduced in premature infants, while average values for the total base, chloride, phosphate and "R" were elevated in premature infants as compared to the control group. The average CO_2 tension for premature infants was within the normal adult range. The range of values for all acid base components in premature infants was much greater than the range of values for the control group, but the individual values and averages are statistically significant at the 1% level as shown in table 7. (The mean values for adults in table 7 include the three individuals eliminated from table 5 who hyperventilated during blood sampling technic.)

There was no statistically significant correlation between birth weight, or age or weight at the time of chemical sampling and pH, CO_2 content, total base, chloride or protein. There was no statistical difference in the acid base values obtained from the infants thought to be entirely well as compared to those infants who were classified as sick. However, it must be remembered that the infants who comprised the "sick" group had mild infections for which they received early, adequate, specific and supportive therapy (see Clinical History). There was no difference of acid base values between premature infants who had received plasma or blood transfusions and the premature infants who had been given no blood or plasma transfusions.

Since there is no statistical correlation of the chemical values to age or weight of the infants, the 92 chemical studies of pH and CO_2 content and calculated pCO_2 on 64 premature infants will be considered as 92 babies, and likewise the 73 acid base studies on 60 premature infants as 73 babies in the following section which will present more detailed

TABLE 7

COMPARISON OF SIGNIFICANT CHANGES IN ACID BASE VALUES OF HEALTHY PREMATURE INFANTS AND ADULTS
(Arterial Blood)

	Mean 16 adults	Mean 60 infants	t†	d.f.	Significance
pH	7.42	7.31	11.24	15.0	<.001
Total CO_2 Content mEq./l.	23.9	20.2	9.64	15.0	<.001
Chloride mEq./l.	102.0	111.0	8.52	15.0	<.001
Prot. Base-Binding mEq./l.	17.0	12.7	18.27	15.0	<.001
Total Base mEq./l.	154.0	159.0	5.50	15.0	<.001
"R" mEq./l.	11.0	15.0	3.01	15.0	<.01
Phosphates (13)* mEq./l.	2.01	4.1	18.44	24.0	<.001

* Values on 13 adults and 13 premature infants.

† The ratio of estimated variances was too great to assume that both samples came from equally variable popuiations and hence the usual Student-Fisher test for the comparisons of means is not applicable. The samples here are smaller than one ought to have for the use of the large sample test in which the variance of the difference of sample means is simply estimated as the sum of their estimated variances. However, an exact test available for such cases (Scheffe, H., On solutions of Behrens-Fisher problem, based on t-distribution, *Annals of Mathematical Statistics*, 1943, vol. 14, pp. 35–44) was used and this gives a t which obeys the Student-Fisher law but with degrees of freedom one less than the smaller sample size.

analyses of the various fractions of the acid base balance. All chemical values of the premature infants which fell within the range for the control group, as shown in table 6, were considered to be normal values, and deviations from the control group are referred to as increased, decreased or abnormal.

Hydrogen Ion Concentration, Total Carbon Dioxide Content and Carbon Dioxide Tension.—Tables 3 and 4 present the results of 92 chemical determinations of pH, total CO_2 content and calculated pCO_2 in the arterial blood of premature infants at weekly or bimonthly intervals. The values for twins are also indicated. These figures reveal that 78% of the infants had an elevated hydrogen ion concentration, i.e., lowered pH.

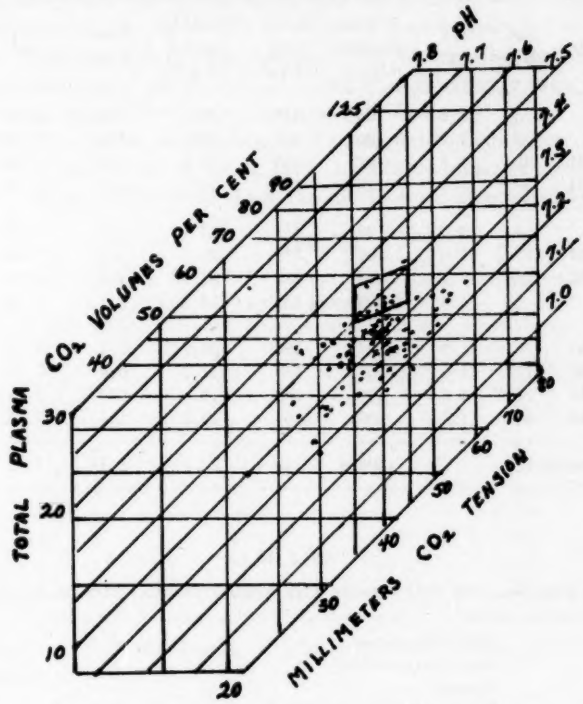
TABLE 8

AVERAGE HYDROGEN ION CONCENTRATION, TOTAL CO_2 CONTENT AND CO_2 TENSION IN ARTERIAL BLOOD OF 92 PREMATURE INFANTS

Premature Infants		pH	Total CO_2 cont. mEq./l.	pCO_2 mm. Hg calculated	Comment
No.	%				
61	67	7.29	19.2	37.8	Metabolic acidosis
12	13	7.38	23.9	39.2	Normal
10	10	7.25	23.7	51.1	Resp. acidosis
6	7	7.43	19.9	29.6	Resp. alkalosis
3	3				Unclassified

Table 8 shows that 67% of the premature infants had not only a lowered plasma pH but a low total CO_2 content as compared to the adult range; that is, an uncompensated metabolic acidosis. Of the remaining infants, 13% had a normal pH and CO_2 content,

10% had a respiratory acidosis, 7% had a primary CO_2 deficit and 3% were unclassified.* The individual values are better illustrated by the traditional Peters and Van Slyke[17] tri-coordinate graphic representation of this data (Fig. 1).



ACID-BASE EQUILIBRIUM OF THE BLOOD PLASMA (Arterial)
Premature infants are represented by dots. Adult controls are represented by quadrilateral.

FIG. 1

Total Base and Chloride.—The total base in 73 premature infants was either within the normal adult range or elevated, but never low. The total base was elevated in 60% of the premature infants and the chloride was elevated in 84% of the infants studied. Only 10% of the premature infants had both a normal total base and normal chloride level in the plasma.

In an analysis of the relationship of normal plasma chloride levels to pH and CO_2 content it is of interest to note in tables 9 and 10 that 9 of the 12 infants with normal chloride had an acidosis.

Twelve of the 92 infants studied had a normal plasma pH, carbon dioxide content and carbon dioxide tension. Seven of these infants also had plasma analyses for chloride and total base. Table 11 reveals that the plasma chloride levels were elevated to an average value of 110 mEq./l. and the total base to an average value of 159 mEq./l.

* Unclassified—refers to infants in whom the blood chemical determinations were not sufficiently definite for placement in a group; i.e., metabolic acidosis or respiratory alkalosis group.

TABLE 9

ANALYSIS OF TOTAL BASE, pH, AND TOTAL CARBON DIOXIDE CONTENT IN ALL BABIES WITH NORMAL PLASMA CHLORIDE VALUES

Name	Hosp.	Age, days	Wt. kg.	Normal chlorides mEq./l.	Total base mEq./l.	Total CO_2 content mEq./l.	Free CO_2	pH	pCO_2 mm. Hg
14Co	HK	3	1.2	106	158	21.1	1.4	7.26	45.0
20Ha	HK	2	1.3	106	161	22.2	1.3	7.32	41.5
27Pa	CHM	40	1.5	101	154	25.6	1.7	7.26	52.5
29Sc	CHM	28	1.9	103	156	23.7	1.6	7.24	53.0
37Ca	HK	6	2.0	99	155	25.4	1.6	7.28	52.0
40Em	CHM	19	1.6	106	155	21.3	1.1	7.34	38.0
43Lo	CHM	22	1.4	106	158	24.5	1.3	7.35	43.0
50Be	UM	5	1.3	105	155	19.2	1.1	7.34	34.5
54Da	CHM	5	1.9	104	156	20.7	1.2	7.33	38.0
58Re	CHM	11	1.9	105	153	12.7	0.9	7.23	29.0
59Va	CHM	14	1.8	99	155	19.9	0.8	7.48	26.5
620d	CHM	44	1.7	103	161	29.1	1.4	7.41	44.5
12	Averages			103.6	156.4	22.1	1.3	7.32	41.5

TABLE 10

ACID BASE BALANCE IN 12 INFANTS WITH NORMAL PLASMA CHLORIDE LEVELS

Metabolic acidosis	6
Respiratory acidosis	3
Normal	1
Respiratory alkalosis	1
Unclassified	1

TABLE 11

PLASMA CHLORIDE AND TOTAL BASE IN PREMATURE INFANTS WITH NORMAL pH AND CO_2 CONTENT

Name	Chloride mEq./l.	Total base mEq./l.
Co #2	111	156
Th	114	166
Wa	108	157
Mc	112	157
Od	111	164
Lo	106	158
Mo	107	157
Averages	110	159

Samples were taken from seven newborn premature infants before any feedings were instituted. It is interesting to note in table 12 that their values for pH, CO_2 content, chloride and total base were similar to older premature infants in the study.

Protein.—All plasma total protein values with one exception were lower than the adult values. This confirms other more detailed studies of protein values.[18]

Inorganic Phosphate.—In 13 infants in which this determination was made, the average inorganic phosphate level was 2.1 mEq./l. higher than the average adult value (table 6). These values are comparable to the values reported by Branning.[4]

"R."—The "R" fraction of the blood for 73 premature infants averaged 15 mEq./l. as compared to 11 mEq./l. for 16 adults. Half this difference may be accounted for by the elevated PO_4 content of the blood. Thus, the alkali reserve is decreased by phosphate and

TABLE 12

VALUES FOR pH, TOTAL CO_2 CONTENT, CHLORIDE AND TOTAL BASE IN FASTING NEWBORN PREMATURE INFANTS

Name	Age, days	pH	Total CO_2 content mEq./l.	Chloride mEq./l.	Total base mEq./l.
4Ba	2	7.23	18.1	117	161
17Fi	1	7.27	20.4	114	170
25Mc	2	7.36	18.7	108	155
30Se	2	7.26	19.5	107	159
63Sm	2	7.21	18.7	111	166
46Ma	1	7.34	23.6	110	157
Averages		7.28	20.2	110.4	161.3

perhaps organic acids in the blood as well as by chloride in those patients in which chloride is elevated.

DISCUSSION

The majority of premature infants in this study showed an increased hydrogen ion concentration, a low carbon dioxide content and a normal or slightly decreased carbon dioxide tension. Neither by clinical evaluation nor by examination of breathing records[19] could evidence of sustained hyperpnea indicating increased alveolar ventilation be noted in these premature infants (no infants with diarrhea, vomiting or evident dehydration were included). On the contrary, one would have expected by the type of their respiration that these infants would have developed a primary carbon dioxide retention with an increased carbon dioxide tension.

It is of interest to note that a few of the infants had a primary carbon dioxide deficit (respiratory alkalosis) indicating either that insufficient carbon dioxide was produced or possibly was driven off by some stimulus to respiration other than the action of carbon dioxide tension on the respiratory center.

Three of the 92 infants studied had prolonged respiratory distress. Two of these infants had respiratory acidosis and one had a normal pH and CO_2 content. However, other infants of the total series who had respiratory acidosis, had no dyspnea, cyanosis or any respiratory difficulties which could be observed clinically or noted on the breathing records. Therefore, the nature of the acid base disturbance could not be anticipated by clinical examination of

the infant. From previous studies, it could be assumed without chemical analysis that any single premature infant would probably show an increased plasma hydrogen ion concentration as measured by adult standards, but the exact increase could not be anticipated. Neither was the hydrogen ion concentration related to the prognosis of the patient, unless extremely high (or, in terms of pH, a value below 7.0). One infant, Sm, who died six hours after sampling, certainly did not betray chemically the obviously grave prognosis evident by clinical examination.

The elevated total base found in 60% of the premature infants is different from previously published data[4,20,21] which have noted values within the adult normal range. This discrepancy may be explained by the fact that some observers arrived at the values for total base by separate analyses of the various fractions or studied smaller series of infants, or used venous blood samples and employed different analytic methods. The present investigators cannot explain the elevated total base found nor its relation to the intracellular metabolism of these infants.

No adequate explanation has been found for the cause of the high plasma chloride found in 84% of the premature infants and which confirms the findings of others. Young et al.[22] found an average serum chloride level of 109 mEq./l. in 8 to 18 day old premature infants. Hoffman et al.[20] noted an average chloride level of 110 mEq./l. and bicarbonate level of 18 mEq./l. in 28 premature infants fed on evaporated milk mixtures. Moreover, Hoag and Kiser[23] and Marples and Lippard[2] have noted that full term infants on breast milk feedings had an increase in plasma chloride (106 and 107 mEq./l., respectively) as compared to adult values. Apparently Branning[4] has been the only observer who found normal serum chloride levels in premature infants.

Hoffman et al.[24] have stated that a "diet of evaporated cow's milk has enough excess of chloride to produce in premature infants a moderate chloride acidosis." The present authors' recalculation of their data[20] from their balance studies reveals that two-thirds of their infants retained more chloride than sodium and one-third of the infants retained more sodium than chloride. The average retention of chloride was 1.27 mEq. more than the average retention of sodium for the total group. However, Darrow et al.[21] in a study found that the ratio of chloride to sodium retention in premature infants receiving a formula of ½ skimmed milk with added carbohydrate (10%) was but 0.6 as compared to 0.7 for those receiving human milk. These values are lower than the values reported for infants fed evaporated milk mixtures.

An acidosis due to a high ingestion of chloride in milk implies that the kidney function is inadequate in its excretion of acid. Young, Hallam and McCance[22] have noted that the renal clearance of sodium and chloride is low in premature infants and that the renal tubules probably reabsorb more chloride and sodium per unit volume of glomerular filtrate than do full term infants. They noted, too, that at all ages in infancy the chloride clearances depend upon the minute volume of urine; i.e., as the minute volume decreases, the chloride clearance falls. Subsequently, Gordon and others[25] have shown that the ingestion of ammonium chloride with an adequate fluid intake in three premature infants was followed by the excretion of a higher average percentage (98%) of the ingested dose than was obtained for a comparable group of full term infants. Since two of the three infants became dehydrated and listless, and the clinical findings could not be correlated with plasma CO_2 content or chloride, or with the presence of inadequate urinary formation of ammonia and conservation of sodium, Gordon suggested that disturbances of acid base balance may be conditioned by disabilities in intracellular metabolism as well as by renal dysfunction.

Four points in the data presented here bear on the question as to whether the chloride composition of the infant feeding is the cause of acidosis in premature infants. 1. The authors were fortunate to have 39 well babies on ½ skimmed milk with added carbohydrate and 22 babies on an evaporated milk formula with added carbohydrate and could not observe any significant difference in the plasma chloride level (111 mEq./l. and 113 mEq./l., respectively) of the two groups. 2. Of 12 infants in this study in whom the plasma chloride level was normal, there were nine infants who had an elevated hydrogen ion concentration. 3. In seven other infants who had a normal hydrogen ion concentration and plasma carbon dioxide content, the plasma chlorides were elevated to an average value of 110 mEq./l. and the total base to an average value of 159 mEq./l. 4. Samples taken from seven newborn premature infants before any feedings were instituted had essentially the same values for pH, CO_2 content, chloride and total base as older infants in the study. In other words, a high plasma hydrogen ion concentration and a low carbon dioxide content may occur without an elevated plasma chloride, an elevated chloride level may occur with a normal hydrogen ion concentration and, furthermore, an elevated plasma chloride level may be found at birth before feedings are instituted. Therefore, although a high ingestion of chloride in milk may be a contributory factor, it is not believed to be the primary cause of the acidosis of premature infants.

Hemo-concentration is an accepted cause for elevated plasma chloride. Three of the 73 infants in this series had markedly elevated plasma chloride, protein and total base, suggesting hemo-concentration as a factor in these particular infants. However, it is interesting to note in table 13 that the hemoglobin in two infants was low[26] for their age, a point against hemo-concentration. In the remaining 70 infants there was no indication by the blood chemical studies that hemo-concentration was the cause of the elevated chloride levels. Fluid balance studies are necessary to settle this question definitely.

TABLE 13

Name	Age, days	Wt. (kg.)	Chloride	Protein	Total base	Hb.
We	4	1.5	120	14.1	168	14.6
Dan	12	1.9	120	15.0	171	
Car	7	1.5	124	15.0	160	14.3

Smith[16] suggests that the redistribution of water and electrolytes which occurs in premature infants is "probably related to endocrinologic processes occurring in the mother and fetus during the last part of pregnancy and suddenly altered at birth." He implies that adrenal cortical insufficiency may be at fault. The present investigators have no evidence from these studies to corroborate or deny this theory.

Although the blood inorganic phosphate is elevated, as shown by this work and others,[4] McCance[27] has shown that premature infants (fed breast milk) have a relatively lower phosphorus excretion than adults. Lewis and others[28] have shown that the excretion of nitrogen and phosphorus was decreased in adult human subjects exposed to a five hour period of anoxia. However, the inorganic phosphorus in the blood was also decreased under the same conditions. No direct analogy can be made between this study and the conditions found in premature infants, but the possible role of chronic anoxia and its relation to mineral metabolism must be considered. McCance[27] states that "if, moreover, it is cor-

rect that infants are in a state of acidosis during the early days of life, the acidosis may be explained by the paucity of phosphates available for excretion, for without them the ability of the kidney to excrete acids, and so to correct an acidosis must be curtailed." However, the elevated plasma inorganic phosphate in premature infants would seem to contradict this possibility. The lower phosphorus clearance, then, would be a plausible explanation in view of the fact that formula-fed babies do have an excessive intake of phosphorus. It is certainly true that in the ordinary patient with severe acidosis due to diabetes, the acidosis is accompanied by excessive phosphaturia, the product of a buffering mechanism. However, this peculiarity of inorganic phosphate metabolism is not necessarily the primary cause of the acidosis. Further work would be required to determine to what extent it contributed to the continued state of acidosis which exists for an indefinite but prolonged time in the neonatal period.

This study does not reveal the cause of the acidosis, but rather presents the broad range of chemical variations that may occur in the blood of well premature infants and offers substantial proof that acidosis is present for at least two months (age duration of this study) in premature infants. The theory[5] that a partial anaerobic catabolism of carbohydrate may result in a lower production of carbon dioxide and an excessive formation of organic acids, and thus an acidosis, must be seriously considered in light of this study.

What are some of the practical clinical implications to be drawn from this data? There seems little justification for the establishment of rigid rules for fluid and electrolyte therapy with our present lack of knowledge of the intra and extracellular metabolism of premature infants. This study has shown that the majority of healthy premature infants have a metabolic acidosis, a small percentage have a respiratory acidosis, and a smaller percentage a respiratory alkalosis, but the majority do well clinically. It seems neither practical nor logical to undertake a program of specific therapy to correct this in otherwise "healthy" infants since this chemical state may be normal for them. If alkali therapy is indicated in cases of severe acidosis, the use of sodium bicarbonate has theoretic advantages over sodium lactate, since sodium bicarbonate seems to be completely metabolized, whereas the lactate of sodium lactate solutions is excreted almost unchanged in the urine.[29] Since base must accompany the urinary lactate excretion, sodium lactate would not seem to be the ideal form of therapy in premature infants.

The increased arterial hydrogen ion concentration in these premature infants suggests that they have a narrower "chemical" margin of safety than do adults. When they undergo any stress such as infection, improper feeding or diarrhea, they can rapidly progress in a matter of hours to a severe acidosis which needs prompt alleviation. Concomitant clinical and chemical evaluation is essential to determine the nature and extent of metabolic changes in sick premature infants. Although our knowledge of the amount of intracellular and extracellular water in premature infants is far from complete, we do know that the ability of the kidneys of the premature infant to concentrate urine is less adequate than the kidneys of adults under the same conditions, and that an early and severe loss of fluid in ill premature infants must be alleviated.

Summary

A study of the acid base balance of arterial blood in 92 premature infants, aged 1 to 65 days and 1.1 kg. to 2.3 kg. in weight, has been presented. The temporal artery blood was analyzed for pH, plasma CO_2 content, chloride, total protein, total base. Alveolar carbon dioxide tension (pCO_2) and "R" were calculated. Acid base analyses on the femoral artery

blood of 16 adolescent well boys were used as controls. The study reveals the following salient facts:

There is a wide variation in the blood chemical findings between normal, well premature infants. In addition, repeat determinations upon the same infants revealed a more labile blood chemical picture than is found in older infants or adults.

No premature infant had all fractions of the acid base balance within the adult normal range.

The mean values for pH, CO_2 content and protein were reduced in premature infants, while the mean values for total base, chloride, phosphate and "R" were elevated as compared to the values for the adult controls. The mean value for carbon dioxide tension was normal.

Sixty-seven per cent of the premature infants had the chemical findings of an uncompensated metabolic acidosis; 13% had a normal pH and CO_2 content; 10% had a respiratory acidosis, 7% had a respiratory alkalosis and 3% were unclassified.

There was no statistical correlation of acid base values to birth weight or age or weight at the time of chemical sampling.

There was no difference of acid base values in infants who had been transfused by blood or plasma and those infants who had never been given blood or plasma transfusions.

By clinical examination alone, the nature of the acid base variations could not be anticipated in what we generally consider as well premature infants. There was no correlation between the variations of the acid base disturbance and the prognosis for life in these babies.

The fact that most premature infants have an increased hydrogen ion concentration and an unstable acid base balance may be additional reasons why premature babies so easily develop severe acidosis when any stress occurs, whether it is improper feeding, infection, etc.

The cause of the acidosis in premature infants has not been established. The theory that premature infants have a partial anaerobic metabolism with a decreased production of carbon dioxide is tenable but not established.

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SPANISH ABSTRACT

Estudios del Equilibrio Acido-Basico en Niños Prematuros

Está bien establecido, que niños prematuros sanos existen en un estado de acidosis. Sin embargo, no ha habido un estudio detallado de una serie grande de niños prematuros en los cuales los siguientes

análisis hayan sido hechos: (1) Estudio de los limites de las variaciones quimicas que pueden ocurrir normalmente en prematuros sanos; (2) estudio de la relacion del dioxido de carbono y el Ph sanguineo con otras fracciones del balance acidobasico; (3) estudio comparativo entre las alteraciones quimicas y el estado clinico del paciente.

Los autores señalan, que los cambios en las concentraciones ionicas de hidrogeno y de dioxido de carbono no podrian interpretarse adecuadamente, sin el estudio concomitante de la fisiologia respiratoria y funcion renal de los prematuros. Unicamente conociendo estos hechos es posible poder interpretar y analizar estas variaciones quimicas y sus factores causativos. Por esa razon, el presente estudio de la fisiologia quimica de los niños prematuros fué realizado.

Se hicieron 92 analisis de Ph; CO_2 total, con determinaciones de la tension del dioxido de carbono de la sangre arterial en 64 prematuros Se completaron 73 análisis acido-basicos en 64 prematuros. Sangre de la arteria temporal fué analizada para Ph, CO_2, cloruros, proteinas totales y bases totales. En otros 13 pacientes el PO_4 fue analizado. La tension alveolar del dioxido de carbono (pCO_2) y "R" fue calculada. Analisis acido-basicos de la sangre de la arteria femoral fueron realizados en 16 adolescentes usados como controles.

Este estudio reveló los siguientes datos salientes:

1. Que las variaciones de los valores quimicos sanguineos de prematuros son enormes.
2. En ningún prematuro se demonstró, que todas las fracciones del equilibrio acido-basico fueran iguales a las obtenidas normalmente en los adultos.
3. El promedio de valores de Ph, CO_2 y proteinas estuvo reducida en los prematuros, mientras que los promedios para los valores de base total, chloride, PO y "R" estuvieron elevados.
4. No hubo relacion estadistica significante entre los valores del equilibrio acido-basico, y el peso al nacer, o la edad del paciente al momento de la determinaciones quimicas.
5. No hubo diferencia en los valores acido-basico entre los casos tratados con transfusiones de sangre y plasma y los casos que no recibieron transfusiones.
6. 67% de los casos tuvieron una acidosis metabolica uncompensada; 13% tuvieron un pH y CO_2 normales; 10% tuvieron una acidosis respiratoria; 7% desarrollaron una alkalosis respiratoria y un 3% de casos fueron unclasificados.
7. La naturaleza de las alteraciones del equilibrio acido-basico, no pudo ser sospechada mediante el examen clinico de los pacientes libres de infeccion, y tampoco estuvo relacionada con el pronostico de vida.
8. El hecho que la mayoria de los prematuros tienen un aumento en las concentraciones de iones de hidrogeno durante los dos primeros meses de nacidos (duracion de este estudio) añade mas evidencia a la idea, de que los prematuros no disfrutan de un margen de seguridad quimica en caso de esfuerzos fisicos sobre-añadidos.
9. La causa de la acidosis en prematuros no esta establecida. La teoria, de que los prematuros tienen un metabolismo anaerobico con disminución en la produccion del dioxide de carbono es defendible, pero no establecida.

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STUDY OF THE INFLUENCE OF SEX OF DONOR ON THE SURVIVAL OF ERYTHROBLASTOTIC INFANTS TREATED BY EXCHANGE TRANSFUSION

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WIDESPREAD interest has been aroused by the recent report of Allen, Diamond and Watrous[1] which stated that the use of female blood for transfusion of erythroblastotic infants improved their chances for survival. This conclusion was arrived at after statistical analysis, no biologic reasons for the beneficial effect having been ascertained. In order to test the validity of this conclusion, study of other series of cases was deemed essential. The present communication is concerned with an analysis of 74 cases of erythroblastosis fetalis, treated by exchange transfusion, which have been studied at the Baltimore Rh Typing Laboratory.

METHODS AND MATERIALS

Most of the mothers of the infants included in this study had had serial prenatal Rh antibody studies. The infants were delivered and treated in a number of hospitals in Baltimore. Samples of the cord blood were examined as promptly after delivery as possible. All immunologic studies were done in the Baltimore Rh Laboratory by methods previously described.[2,3] The hematologic studies were done in the hospital where delivery occurred.

Only those infants who received 150 cc. or more (150 to 800 cc.) of Rh-negative whole blood are included. This lower limit was selected merely to make the present series more nearly comparable to that of Allen, Diamond and Watrous. It is recognized that the use of 150 cc. of blood cannot be considered adequate for a complete exchange transfusion. The sources of blood were (a) a special O Rh-negative blood bank maintained by the Baltimore Rh Laboratory and (b) hospital blood banks throughout the city. All female Rh-negative blood used for exchange transfusion was free of Rh antibodies.

RESULTS

A summary of the results obtained is presented in table 1. The over-all mortality rate in the 74 cases was found to be 17.6%, a figure not statistically different from the rate of 15% obtained by the authors previously cited.† Fifty-five of the infants received either male or female blood alone. Three received blood from both male and female donors. In 16 cases it was not possible to ascertain with accuracy the sex of the donor. Subsequent analyses in this communication are based entirely on the 55 cases in the first category, the pertinent details of which are listed in table 4.

In the group of 23 infants who received blood from female donors, there was a mortality rate of 21.8%. This finding is in marked contrast to the 100% survival of 42 infants in the Boston series who received female blood. The mortality rate in the 32

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† $x^2 = 0.0987$. (A statistically significant figure for x^2 is 3.84.)

infants receiving male blood was 12.5%, as compared to 19.7% in the Boston series. It will be noted that in the present study the mortality rate when male blood was used actually appears to be lower than when female blood was used, but statistical analysis shows no significant difference.*

In view of the divergence in results, further examination of the two series was under-

TABLE 1

RELATION OF SEX OF BLOOD DONOR TO MORTALITY

Sex of Donor	Outcome		Totals	Mortality Rate %
	Survival	Death		
Female	18	5	23	21.8
Male	28	4	32	12.5
Male and Female	3	0	3	0.0
Unknown	12	4	16	25.0
Total No. of Cases	61	13	74	17.6

taken in an effort to explain the discrepancy. It became apparent that the ratio of male and female bloods used in the severely affected cases offered a possible explanation. This suggestion led to an attempt to compare both groups in respect to the severity of the disease. Because clinical characterization of the cases as mild, moderate and severe was

TABLE 2

COMPARISON OF DISTRIBUTION OF MALES AND FEMALES ACCORDING TO SEVERITY OF DISEASE (INITIAL RED BLOOD COUNT)

Series	Red Blood Count	Sex of Donor		Approx. Ratio of
		Male	Female	Male:Female
Baltimore	Over 3 million	20	9	2:1
	3 million or less	8	8	1:1
Boston*	Over 3 million	55	26	2:1
	3 million or less	59	12	5:1

* Taken from Table 8 of Allen, Diamond and Watrous.[1]

considered too variable a quality to be used for comparison, they were classified on the basis of the initial red blood count, a more objective criterion of severity (table 2). The level of 3 million red cells/cmm. was chosen as a dividing line only because Allen et al. used this standard. The authors realize that a red cell level of 3 million or more may include infants who are severely ill.

Table 2 indicates that, in the group of infants with red blood counts over 3 million, the two series are similar in the proportion of male and female blood used. In the group

* $x^2 = 0.296$.

with counts of 3 million or less, however, male blood was used five times more often than female in the Boston series. In the present study they were used in equal numbers. An explanation for the preponderant use of male blood for sicker babies was suggested by Allen et al. as being due to a tendency to select blood with higher hematocrits, all other factors being equal, for such cases. This would result almost invariably in the selection of male blood. In the Baltimore series the equal use of male and female blood for severely affected infants may be due, in part, to a greater tendency to select female blood since the publication of the cited paper. A further analysis, omitting cases treated since December 1949, however, in no way altered the results presented below.

When the mortality rates of the various groups, divided as above, are considered (table 3), there is no significant difference between male and female blood in the mild

TABLE 3

COMPARISON OF MORTALITY RATES FROM 2 CLINICS, USING RED BLOOD COUNTS AS INDEX OF SEVERITY

Series	RBC	Donor Sex	Outcome		Mortality %	x^2†
			Lived	Died		
Baltimore	Over 3 million	Male	19	1	5.0	0
		Female	8	1	11.1	
	3 million or less	Male	7	1	12.5	0
		Female	6	2	25.0	
Boston*	Over 3 million	Male	51	4	7.3	0.63
		Female	26	0	0.0	
	3 million or less	Male	40	19	32.2	3.75
		Female	12	0	0.0	

* Taken from Table 8 of Allen, Diamond and Watrous.[1]

† Yates' correction for small series had been applied to the x^2 values.

cases of either series. The results in the severe cases of the Boston series suggest a difference, since x^2 approaches significance at the 5% level. It is a striking fact, however, that the highly significant x^2 value of 9.73 obtained by Allen et al. from their over-all data has been reduced to 3.75 when only the severe cases are considered. When due allowance is made for the preponderant use of male blood in the severe cases, the evidence for a beneficial effect of female blood is no longer conclusive. The difference between male and female blood in the severe cases of the Baltimore study is not significant. Considering both series it appears that any advantage to the use of female blood is rather dubious.

SUMMARY

An analysis of 74 cases of erythroblastosis fetalis treated by exchange transfusion has been presented. The over-all mortality was 17.6%, a figure comparable to the 15% rate of the Boston group. No advantage for the use of female blood in exchange transfusion was found. It is suggested that the disparity between these data and those of Allen et al. may well be due to the preponderant use in the latter series of male blood for infants severely affected by erythroblastosis fetalis.

TABLE 4

PERTINENT DETAILS OF 55 CASES OF ERYTHROBLASTOSIS FETALIS RECEIVING EITHER MALE OR FEMALE BLOOD ALONE

Case No.	Previous History of E.F.	Duration of Pregnancy (Wk.)	Highest Prenatal Maternal Titers (units)*	Sex of Baby	Coombs Test	Hematologic Data			Jaundice	Hepato Splenomegaly	Sex of Donor	Am't of Trans. (cc.)	Outcome	Remarks
						Hgb.	RBC	NRC/100 WBC						
1. M.D.	No	40	96	M	N.R.	11.6	4.2	2	Yes	0	M	?	Lived	"Partial" exchange at 2 days
2. E.E.	No	40	48	M	2+	?	3.00	Num.	Yes	2+	M	300	Lived	Pale and lethargic at birth.
3. M.M.	No	40	512	M	N.R.	3.5	2.78	?	Yes	2+	M	500	Died	Died at 21 hr. severe E.F., cerebral edema
4. L.N.	Yes	36	48	M	N.R.	?	5.00	1	Yes	2+	M	450	Lived	
5. J.T.	No	36	192	M	N.R.	10.2	3.16	?	Yes	0	M	400	Lived	
6. E.C.	Yes	40	192	F	1+	15.0	3.9	8	Yes	3+	M	440	Lived	
7. M.C.	No	40	3,072	M	4+	11.0	3.1	13	Yes	2+	M	750	Lived	
8. E.J.	Yes	40	256	M	N.R.	6.0	?	90	No	4+	F	380	Died	Edematous. Died during exchange.
9. G.K.	No	40	512	M	2+	13.5	3.0	45	Yes	3+	M	387	Lived	
10. M.L.	Yes	40	384	M	3+	17.5	?	40	Yes	1+	F	400	Lived	
11. M.P.	Yes	39	6,144	M	N.R.	15.0	?	?	Yes	2+	M	750	Lived	
12. E.R.	No	37	256	F	N.R.	13.0	?	75	Yes	1+	M	600	Lived	Premature; 2400 gm.
13. G.B.	No	40	512	M	1+	14.4	3.4	42	Yes	3+	M	725	Lived	
14. E.C.	No	40	2,048	M	4+	13.0	3.39	26	Yes	3+	M	520	Lived	
15. M.D.	No	40	768	M	4+	10.0	2.5	12	Yes	2+	F	550	Lived	Pale and listless at birth
16. H.D.	No	39	384	M	4+	11.3	3.22	54	Yes	1+	F	500	Died	Probable kernicterus, no autopsy
17. L.G.	No	38	384	M	3+	17.6	4.71	?	Yes	2+	M	590	Lived	
18. M.H.	No	38	384	F	4+	15.0	4.19	8	Yes	1+	M	500	Lived	
19. R.I.	Yes	40	12,288	M	4+	10.0	2.7	66	Yes	2+	F	400	Lived	Listless and severely jaundiced at birth
20. F.K.	No	40	1,024	M	4+	17.5	5.9	?	No	1+	F	230	Lived	
21. O.M.	No	40	768	F	N.R.	17.0	?	5	Yes	2+	F	710	Lived	
22. M.R.	No	40	2,048	M	N.R.	13.0	4.1	13	Yes	0	M	800	Lived	
23. H.R.	Yes	40	256	M	3+	16.0	5.6	15	Yes	1+	M	500	Lived	
24. G.Th.	Yes	40	768	M	4+	16.5	5.05	16	Yes	1+	F	500	Lived	
25. G.To.	No	40	384	F	4+	11.0	2.7	28	Yes	2+	F	610	Lived	C. section (obst. reason)
26. D.W.	Yes	38	768	M	4+	14.5	2.85	210	Yes	3+	M	605	Lived	

* Albumin agglutinins.

TABLE 4 (*Continued*)

Case No.	Previous History of E.F.	Duration of Pregnancy (Wk.)	Highest Prenatal Maternal Titers (units)*	Sex of Baby	Coombs Test	Hematologic Data			Jaundice	Hepato Splenomegaly	Sex of Donor	Am't of Trans. (cc.)	Outcome	Remarks
						Hgb.	RBC	NRC/100 WBC						
27. B.F.	Yes	38	12,288	M	4+	10.5	3.07	15	Yes	3+	F	600	Lived	Elective C. section (rising titer) Mother treated with Rh hapten
28. J.B.	Yes	40	384	F	N.R.	13.0	4.04	7	Yes	1+	M	200	Died	Cause of death? Mother treated with ethylene disulfonate
29. C.B.	Yes	40	192	M	4+	13.3	3.53	57	Yes	2+	M	?	Lived	
30. D.C.	Yes	?	3,072	M	N.R.	11.6	4.00	?	Yes	3+	M	500	Lived	C. section (obst. reason)
31. M.C.	No	38	512	F	4+	10.8	3.0	50	Yes	4+	M	450	Lived	Jaundiced and edematous at birth
32. D.D.	No	38	16,384	F	4+	9.9	?	?	Yes	0	F	450	Lived	Elective C. section (rising titer)
33. C.F.	Yes	38	3,072	F	N.R.	15.9	5.0	385	Yes	4+	F	625	Lived	Elective C. section (rising titer) Hr′ sensitization
34. C.G.	No	40	192	F	4+	10.3	3.6	14	Yes	1+	F	250	Lived	
35. E.H.	No	40	384	F	N.R.	10.2	4.0	60	Yes	0	M	500	Lived	
36. M.J.	Yes	36	192	F	4+	9.1	2.64	68	Yes	2+	F	410	Lived	Premature; 1900 gm.
37. J.L.	Yes	40	4,096	M	N.R.	8.2	1.84	527	Yes	4+	M	500	Lived	Marked edema at birth
38. E.M.	Yes	40	2,048	M	4+	12.5	3.00	?	Yes	4+	F	?	Died	Died during exchange, pulmonary edema.
39. D.M.	No	40	3,072	M	N.R.	8.2	3.00	105	Yes	3+	F	650	Lived	
40. D.O.	No	40	384	F	4+	5.0	1.8	50	Yes	4+	F	200	Died	Lethargic and pale at birth, died during exchange.
41. M.P.	No	40	3,072	M	4+	7.8	2.94	64	Yes	3+	M	250	Lived	Severe E.F., cyanotic at birth
42. A.R.	No	40	384	F	2+	9.3	3.3	?	Yes	0	M	380	Lived	C. section (obst. reason)
43. M.W.	No	40	6,144	M	4+	7.3	1.3	153	?	?	M	?	Lived	Severe E.F.
44. H.K.	No	40	8,192†	M	0‡	10.5	3.28	51	Yes	1+	M	550	Lived	Hyperimmune anti-B agglutinin
45. M.N.	Yes	38	4,096	F	4+	11.1	3.42	458	Yes	2+	F	?	Lived	
46. K.M.	No	40	1,536	M	4+	12.0	3.9	10	Yes	1+	M	520	Lived	
47. M.B.	No	40	384	M	4+	11.0	3.5	50	Yes	2+	F	480	Lived	
48. R.C.	No	40	768	M	4+	11.0	3.0	25	Yes	1+	F	550	Lived	
49. A.A.	No	39	384	F	4+	11.6	3.06	?	Yes	0	M	?	Lived	
50. D.T.	No	38	6,144	M	4+	12.2	?	Many	Yes	4+	M	190	Died	Hydropic at birth
51. A.N.	No	38	768	M	4+	15.0	5.2	25	Yes	1+	M	210	Lived	
52. M.B.	No	40	384	F	3+	11.9	4.1	44	Yes	1+	F	500	Lived	Mild edema at birth
53. G.G.	No	40	96	M	N.R.	13.0	?	6	Yes	0	M	?	Died	Cause of death?
54. M.V.	No	36	3,072	M	4+	?	?	?	Yes	2+	F	300	Died	Hydropic at birth, C. section (obst. reason)
55. L.T.	Yes	36	384	F	2+	11.5	?	29	Yes	2+	F	?	Lived	

† Serum titers.
‡ The Coombs test has regularly been negative when anti-A or anti-B is involved.

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SPANISH ABSTRACT

Estudio de la Influencia del Sexo del Donante en la Sobrevivencia de Infantes con Eritroblastosis Fetalis Tratados con Tranfusiones de Substitucion (Exchange Transfusion)

Se presenta un análisis de 74 casos de eritroblastosis fetalis tratados con tranfusion de substitucion (exchange transfusion). La mortalidad general fué de 17.6%, cifra comparable al 15% obtenida en el grupo de Boston. Los autores no encontraron ventaja alguna con el uso de sangre de donantes del sexo femenino en la transfusion de substitucion. Se sugiere que la disparidad entre estos resultados, y los del grupo en Boston, pueden ser debidos a el uso preponderante de sangre de donantes del sexo masculino en niños afectados seriamente con eritroblastosis fetalis.

University of Maryland School of Medicine

‡ The Coombs test has regularly been negative when anti-A or anti-B is involved.

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SPECIAL SECTIONS

THE PEDIATRICIAN AND THE PUBLIC

AN OPEN FORUM

PAUL A. HARPER, M.D., *Editor*

Statements appearing in this column do not necessarily reflect the opinion of the editor nor are they to be interpreted as the official opinion of the Academy.

COMMUNICATIONS FROM I. S. FALK, BORDEN S. VEEDER, M.D., AND HUGH C. THOMPSON, M.D.

The first communication is from Mr. I. S. Falk, Director of the Division of Research and Statistics in the Federal Security Agency. The second letter is Dr. Borden S. Veeder's answer to Mr. Falk. The question under discussion is the effect of capitation payments for pediatric service which was first raised by Dr. Veeder in the April issue of this column. This matter is an extremely important one both for pediatricians and for the public whom they serve.

The third letter is from Dr. Hugh C. Thompson, of Tucson, Arizona, and is an extension of remarks which he made about this column in the February issue.

DEAR DR. HARPER:

I have read with much interest the important and stimulating letter by Dr. Borden Veeder in the April issue of PEDIATRICS (pp. 739-741), and would like to make some comments on it.

Dr. Veeder calls attention to the fact that changes are occurring in every phase of our social and economic life, including medicine. He expresses the opinion that the time has come to think in a detailed way rather than only in general terms about changes in the method of paying for medical care. He discusses the potential effects of capitation payments for pediatric service and decides that the method is impractical. Coupled with reservations about compensation on a salary basis, except in unusual situations, Dr. Veeder concludes that "under any national medical program on an insurance or taxation basis that might eventually develop in this country the fee-for-service method of remuneration would prob-

ably be the only method under which pediatric practice as we now have it would survive."

This conclusion was a surprise to me, because I had understood that capitation payment (or "annual service charge") has long been used in non-insurance pediatric practice, more than in most fields of specialization or "special attention"; and I had supposed it could be used for pediatrics in both voluntary and compulsory insurance plans.

Dr. Veeder argues that the relatively large number of services provided per child demands (a) a smaller number of potential patients per physician serving children and (b) a higher capitation rate for children (or for the practitioner serving children) than would apply to the practitioner serving all ages. Believing that different capitation rates among practitioners serving different members of the family would not be practical (and there being objections against a salary basis), Dr. Veeder is left only with fee-for-service.

The first basic point in Dr. Veeder's argument concerns the amount of service furnished per child. He said:

"[A panel] composed of children would have to be much smaller than a panel including all ages. A third of the work of the general practitioner is with children, as disclosed by the 'Survey.' Thus 33% of the daily work would be with less than 20% of the total individual patient load of a panel. From this it can be calculated that the same amount of medical work would be required for a panel some 40 to 50% smaller if it were made up of children, as for a panel made up of all ages as it is in Great Britain. This would necessitate a different capitation fee."

The Academy "Survey" found, among general practitioners, an average daily case load of 16.4 patients of all ages, of which children accounted for 4.8 per day or 20 per cent (Supplement, tables 38 and 40). In the survey period, children under 15 were about 26 per cent of the total population (Census Bureau estimates for 1946 and 1947). Thus, the disproportion of children among total patients was not as 33 is to less than 20 (as Dr. Veeder thought), but as 29 is to 26. It is doubtful that this disproportion is in itself large enough to support the important conclusion concerning a smaller number of potential patients to be served and a higher capitation rate for children than for others.

Older studies of service loads in the general population do not show for the general practitioner a higher-than-average number of home and office services for children than for the population as a whole (e.g., Collins, *Public Health Reports,* 1940, vol. 55, p. 1985). When using the data of such older studies or of the Academy "Survey," it is important to keep in mind that the service load (total, or distributed by age) observed in the absence of widespread insurance does not give a wholly reliable index of the load to be expected with insurance of broad coverage. With insurance, total load increases and its age distribution may also change. Experience under insurance, voluntary or compulsory, is the best guide on what to expect in insurance practice. I have not found, in the available studies of voluntary insurance operations in the United States, grounds for expecting a higher-than-average load for the age group under 15 (see, for example, Klem, Hollingsworth and Miser, *Medical and Hospital Services Provided Under Prepayment Arrangements: Trinity Hospital,* our Bureau Memorandum No. 69, table 10).

It is, of course, possible that in a widespread insurance program, whether voluntary or compulsory, there would be an appreciably higher attendance load for children than for adults. And that this would place a disproportionately heavy per-capita load on the general practitioner who has a large proportion of children among his parents, and of course on the pediatrician. In this situation, a higher-than-average capitation payment for

children would be justified. Indeed, the capitation rate might need to be graduated by age within the first 15 years of life and especially with respect to the first years. Such graduation would complicate matters somewhat; but I think it is safe to say that it would not be administratively serious or unmanageable.

The second basic point in Dr. Veeder's argument concerns differentials in the rates of payment for general practitioners and qualified pediatric specialists. It is always assumed that there would be such differentials in an insurance system which pays for specialist as well as general practitioner services—whatever the method of payment, and that this would apply to pediatricians as well as to other qualified specialists. For example, in my own studies of cost estimates for a general insurance program, I assumed twice as high average annual incomes for fully qualified specialists as for general practitioners (e.g., *Medical Care Insurance,* 1946, p. 55). Obviously, this would mean higher rates of payment for such specialists than for general practitioners, whether the payments are by fee-for-service, salary, capitation or some combination of methods.

Dr. Veeder asks the question; "Could two practitioners, one in general practice and the other in pediatric practice, live and work harmoniously side by side, with a different capitation payment?" Isn't the answer "yes"—just as harmoniously with different capitation payments as with different fees for office, home or hospital services in present-day non-insurance practice or in future insurance practice?

As I have stated elsewhere (*Medical Care Insurance,* 1946), I hold no general brief for one method of payment for insurance services as against another. These comments on Dr. Veeder's letter are not intended to be a pleading for capitation payments. They are intended only to invite further consideration of this method of payments in pediatrics.

May I close with my word of appreciation for this "open forum," an invaluable resource provided by PEDIATRICS for the discussion of topics that concern the public and the pediatrician.

I. S. FALK
Director, Division of Research and Statistics
Federal Security Agency
Social Security Administration
Washington, D.C.

DEAR DR. HARPER:

Mr. Falk sent me a copy of his interesting discussion of my communication in the April issue. I am delighted that it came to the attention of and interested the Federal Security Agency.

First as to the statistics, in which Mr. Falk finds a 29 to 26 ratio as compared with mine of 33 to 20. I did not go into details in my communication as to how my ratio was obtained as I was trying to keep it brief, and so it was omitted in the final draft of the letter sent for publication. The '33 per cent' was taken from page 48 of the Study report. "Thus about a third of general practice was concerned with the field of childhood." The figures given are 5 in 16 which came out to 31.2 per cent. I used, as the report did, the rounded figures of a third, or 33 per cent. In calculating the child population the 1945 census figures were used, as these were used in the report (page 12), for calculating the child population. The combined figure for the Under 5, 5-9, and 10-14 age groups was 35,131,818 children in a total population of 139,585,518. This comes out close to 26 per cent, as Mr. Falk calculates.

However, I took another matter into consideration in arriving at the figure of 20 per cent. That is that one third of the *work* of the practitioner is with a one fifth segment of the population. Medical work with children is not divided equally with the same load at each age period. My own estimates, and those of pediatric friends with whom I have discussed the question, are that from 65-75 per cent of the children seen by the physician are in the under 5 year group, from 20-25 per cent in the 5-9 year group, and that less than 10 per cent are in the 10-14 year group. The reasons for this are so well known that I need not discuss them. In 1945 there were 24,361,788 children under 10 years of age which was 17.6 per cent of the population. Thus roughly 90 per cent or more of the 'average 5 in 16' are in this 17.6 per cent group. As none of these figures can be regarded as exact, I simply rounded the two into one third of the work of a practice being in one fifth of the population, as such rounded figures are easier for a reader to grasp. Hence the conclusion that a panel made up of children would have to be considerably smaller than a general panel. Further I omitted a discussion of such factors as the longer length of time it takes to 'see' a child as contrasted with an adult in order to shorten the letter. The pediatrician always has two patients—the mother as well as the child he examines.

The crux of my communication was whether or not the pediatrician, practising pediatrics as the vast majority do in the United States, would be regarded as a specialist or a general practitioner under a national medical insurance plan. This, as I pointed out, is a form of practice unique to American medicine and without parallel in the countries where national plans have been developed. It is obvious that a small minority of pediatricians in full time teaching or hospital positions would be in the category of the specialist as he now is under the various systems in Europe, and would be remunerated by salary. But what would happen to the large majority of pediatricians? This is the thing we must think about and the question I raised. In the April communication I gave the reasons why I consider him so essential to the best type of medical care for children. If the pediatrician were placed in a panel capitation system of remuneration, I contend the panel would have to be much smaller than the panel of a general practitioner if the American child now under a pediatrician's care was to continue to receive as good medical care as he now receives. This would require a higher capitation fee. I have merely expressed my own personal opinion as to physicians working side by side with different sized panels with a different capitation fee. Nothing more than an opinion is possible on this point. Mr. Falk brings up the point that a higher-than-average-capitation payment for children might be justified. I am delighted that my communication has opened up this line of thought on the part of those who would have the administrative authority under a national compulsory medical insurance plan.

One last point. In Mr. Falk's third paragraph he refers to the "annual service charge" in non-insurance pediatric practice. I believe he is referring to the plan that has been in limited use in some parts of the country where the pediatrician agrees for a fixed fee to supervise the baby's growth and development (including immunizations) for the first year of life. It, according to the limited information available to me, does not include medical fees for an illness such as a pneumonia, but only feeding adjustments and the like. This is an excellent example of "fee for service" remuneration, similar to the inclusive fee of the obstetrician for "prenatal, delivery and post partum care."

May I take the opportunity, in view of the personal letters from others, to state I am not in favor of nor advocating a national compulsory medical insurance plan, as in my opinion it would lower the quality of medical care. Nor do I think the development of

such a plan is imminent. It is in my thinking, however, that such a plan will be developed when a period of depression sets in. Moreover, such a period is bound to come sooner or later, and it will be a bad one as a result of the economic shenanigans of the "New Deal" and "Fair Deal." For this reason I feel that it is most important for physicians to be thinking temperately and unemotionally of the details which will be involved in such a plan.

BORDEN S. VEEDER, M.D.
St. Louis

DEAR DR. HARPER:

Dr. Richmond's letter in the June number of PEDIATRICS has just come to my attention. Dr. Richmond has obviously misinterpreted my letter, and if you are willing I would like to correct his impression.

I did not attack the propriety of presenting minority opinions in "The Pediatrician and the Public." My objection to the column as it had been conducted, and I may say that my criticism does not apply to the last several issues, was that there was very little expression of the opinions held by the majority of the members regarding socialized medicine or solutions of the problem of medical care of all which would be acceptable to the majority. Having belonged to minorities at various times, I certainly agree that they should have their say, but at the same time I felt that the official organ of the Academy should reflect clearly enough the feelings of the majority, so that it would not appear that the Academy itself was socialistically inclined.

Dr. Richmond also questions my statement that the management of the Academy was *previously* not democratic. This was based on the fact that until the last two years the individual members in some states were not consulted regarding the selection of state chairmen for their states. It is to be noted that only single nominations for district chairmen, alternate district chairmen, and higher officers, are now presented to membership for voting. There may be very good arguments in favor of this procedure, but it is not democratic. I will gladly admit, however, that there has been a very noticeable trend toward democracy in the administration of Academy affairs during the last two or three years.

HUGH C. THOMPSON, M.D.
Tucson, Arizona

TRENDS

By JOHN P. HUBBARD, M.D., *Contributing Editor*

This and subsequent descriptions of events and trends are intended to be unbiased and factual, presenting both sides of controversial matters so that conclusions may be formed from critical appraisal of things as they are. These statements do not necessarily reflect the opinion of the writer nor are they to be interpreted as official opinion of the Academy.

INCREASE IN CHILDREN'S BUREAU FUNDS

WITH the war situation and the mobilization of medical manpower taking a prominent position in legislation directly affecting the medical profession, very few of the unprecedented number of health bills introduced into the 81st Congress have been enacted into law. But one piece of legislation which has been passed is of particular interest to the pediatric group since it provides for a large expansion in the grant-in-aid program of the Children's Bureau. The 1950 amendment to the Social Security Act (H.R. 6000) has nearly doubled the federal funds available for maternal and child health services, crippled children's services, and child welfare services.

The remarkable growth in this program is brought into clear focus by the increases which have been made in the allocations to the Children's Bureau since the enactment of the Social Security Act in 1935. Under the provisions of the original act an annual budget of $8.17 million was allocated for grants-in-aid; $3.8 million for maternal and child health services, $2.87 million for crippled children's services, and $1.5 million for child welfare services. Each of these categories was increased in 1939 to a total of $11 million, increased again in 1946 to a total of $22 million and now to $41.5 million. The increases which the 1950 amendment allows for each of the three parts of the grant-in-aid program are as follows: for maternal and child health from $11 million to $16.5 million, for crippled children's services from $7.5 million to $15 million and for child welfare services from $3.5 million to $10 million.

In a news release from the Federal Security Agency, under date of August 28, 1950, Miss Katherine Lenroot predicts that many thousands of children will have greater chance for good health and care when the increase in grants gets in operation: "Each state develops its own plan for using federal grants, taking into account the available resources whether under private or public auspices. As a result, no two state plans are alike. For this reason it is impossible to predict exactly which children and how many of them will benefit from the increased grants under the 1950 amendment. The fact that there will be many thousands who will be helped can be seen clearly from the reports for the year 1949 when much smaller grants were available."

In 1949, maternal and child health services—financed at least in part by federal funds—can be judged from the following data: over 683,000 infants and pre-school children attended well child clinics; doctors made 2,246,000 examinations of school children; over 1,560,000 children were immunized against smallpox; 1,547,000 children were immunized against diphtheria; approximately 168,000 mothers attended prenatal clinics during pregnancy, and approximately 56,000 received medical examinations after delivery. In the crippled children's program, all states operate diagnostic clinics where a child with a handicapping condition may be brought for diagnosis free of charge. Within

the limits of available funds states provide treatment for some crippled children including medical care, hospitalization and convalescent care. A large number of these children are those needing orthopedic or plastic treatment. Most states do something also for children with other crippling conditions such as rheumatic fever, infantile paralysis, cerebral palsy, epilepsy and hearing defects. In 1949 over 200,000 children received professional services from doctors, nurses, medical social workers, physiotherapists and others. Nearly 80,000 crippled children were brought into these programs for the first time. About 150,000 received diagnosis or treatment at clinics, approximately 350,000 received hospital care and about 5,300 received convalescent home care. The child welfare services, which are essentially social services for children, were given to 231,000 children in 1949.

With the increased funds now available we may expect to see an immediate expansion of these federally supported services for children. Since a great deal of interest is now centered on school health services, these services will undoubtedly be given high priority, both from the point of view of increasing services where they are now sparse or altogether lacking and also from the point of view of studying the effectiveness of the methods which are being used. Services for crippled children will be increased especially in categories that have heretofore been limited because of lack of funds, such as epilepsy and cerebral palsy. We may hope also that increased efforts will be directed against the devastating effects of accidents which far outnumber all other causes of death in the childhood years.

PUBLIC HEALTH, NURSING AND MEDICAL SOCIAL WORK

MYRON E. WEGMAN, M.D., *Contributing Editor*

RECENT ADVANCES IN RABIES

EVERY practicing pediatrician is faced with the problem of possible rabies in children bitten by animals. This terrifying and dramatic disease, of world-wide distribution and concern, has been the object of research in many countries. Following an International Rabies Conference in Paris in 1927, data concerning 1,600,000 persons treated were collected by the Health Organization of the League of Nations. Final proof of the value of Pasteur treatment could not, however, be obtained, as no evidence was available to compare the outcome of the disease in treated and untreated individuals.

After discussion at the First World Health Assembly in 1948 rabiologists all over the world were consulted by the World Health Organization through a questionnaire, and an expert committee was convened in Geneva from 17 to 22 April, 1950, to examine the replies received, review the newest developments, and make recommendations. Highlights of the report of this Expert Committee are presented in the *Chronicle* of the World Health Organization, vol. 4, no. 9, pp. 278-284, September 1950.

ACTIVE IMMUNIZATION

Since Pasteur first used his vaccine in attempts at therapy major activity has been directed at two objectives—treatment of the exposed human beings and mass immunization of animals. "Differences which are known to exist in the biological quality of antirabies vaccines have thrown doubt on the value of current vaccination procedures. It is now well established that, while certain batches of vaccine show a suitable potency, others, prepared under seemingly identical conditions, appear to be of little value."

MOUSE POTENCY TEST

"Improvement of vaccines in current use and production of a vaccine of standard potency became possible when Webster introduced a specially bred white Swiss mouse as testing animal. These mice are cheap, easy to breed, and highly susceptible to rabies. Later, Habel developed a standardized mouse potency-test . . . based on a series of immunizing injections of constant concentration and quantity which are followed by intracerebral challenge of tenfold virus dilutions on the 14th day. Mice are observed for another two weeks and then the 50% mortality endpoints are determined. A thousandfold difference in protection between controls and vaccinated animals is the minimum protection required."

Use of this technic has established the need of a titre of at least 10^{-6} in brains to be used for vaccine and has elucidated many technical production factors. It appears essential to submit samples of each batch of vaccine to a central laboratory for potency testing to ensure dependable vaccine.

ULTRAVIOLET (UV) IRRADIATED VACCINE

"Rabies vaccines inactivated by ultraviolet irradiation have consistently given high pro-

tection values in the mouse potency test. The titres are usually significantly higher than those obtained with other vaccines in current use. It has been found that as much as five times the minimal inactivating exposure has to be given before denaturation of the antigen takes place. There exists, therefore, a broad margin in which it is possible to work safely. . . . Apart from an initial drop in titre, dried preparations keep their antigenicity well and can be recommended for use in countries where production and storage facilities are not adequate. The 'UV vaccine' is now used for about half of the patients coming for treatment in the USA. This number is estimated at about 15,000."

Chick Embryo Vaccine (Flury Strain)

"A street virus recovered from a human case (Flury) has been subcultured in chicken and later adapted to chick embryos. In the course of numerous passages this strain has completely lost its pathogenicity for dogs, when given by routes other than the intracerebral one. The embryo itself, finely ground and freeze-dried, constitutes the vaccine. Large-scale trials in dogs, in the USA, have given very promising results. Not only is the vaccine innocuous for dogs, but it also shows some promise of conferring immunity for a longer period than other vaccines used so far. In experiments on a few human volunteers (cancer patients) it proved itself to be innocuous, even when given in high doses. "This vaccine cannot be tested with Habel's mouse potency-test. A special test, carried out on guinea-pigs, had to be developed. These are immunized by intramuscular injection and challenged after three weeks with street virus given intramuscularly."

Paralysis-Producing Factor

Occurrence of paralysis following the use of rabies vaccine has been the most serious complication of this procedure. Paralysis has occurred with sufficient frequency to constitute a strong deterrent to use of the vaccine on casual indication. The early assumption that paralysis was due to infection with fixed virus contained in the vaccine was dropped when paralysis was observed after use of completely killed vaccine. "Experiments in animals led to the discovery that similar symptoms and pathological changes in the central nervous system could result from serial injections of normal brain tissue. A systematic test was developed to check these somewhat irregular occurrences, as it was found that the addition of adjuvants—lanolin, and paraffin oil, with killed BCG bacilli or *Mycobacterium butyricum*—to one dose of normal brain resulted fairly consistently in paralysis of the experimental animal. This test is now applied to rabies vaccines to determine the content of paralysis-producing factor.

"Successful attempts have been made to eliminate this factor from rabies vaccines by subjecting them to benzene extraction from the dried state. The remainder of the benzene is removed by ether treatment and the dried sediment taken up in calcium acetate. The washed sediment constitutes the final product. At present work is being carried out with a view to the production of this vaccine on a commercial scale."

Passive Immunization

Hyperimmune Antirabies Serum

Injection of rabies vaccine in a presumably infected person is one of the few examples of primary active immunization as a prophylactic measure. Theoretic and practical advantages in passive immunization have stimulated search for an effective serum for more

than 50 years. "Reports have been partly favourable, particularly as to the use of a sero-vaccine, and partly discouraging.

"In recent years, modern methods of purification and of concentration of the antirabies serum fractions containing the neutralizing antibodies, have made possible the preparation of hyperimmune serum. This serum is obtained by repeated injection of fixed strains of rabies in rabbits or sheep. The animals are bled at regular intervals and large pools of serum or plasma prepared. These are fractionated (by such substances as ammonium sulphate, sodium sulphate, or methanol) and the gamma, or beta and gamma, globulin fractions concentrated. The original neutralizing antibody titre has thus been increased a thousandfold, while at the same time the protein level was maintained at the normal value of 7%. With this serum, results have been obtained in animals which are superior to any results obtainable with vaccine alone. Protection was afforded only when serum treatment was given not later than 72 hours after infection. Optimal protection was obtained when serum treatment was followed by a course of vaccine. No interference between passive and active immunity has been observed. Serum treatment suggests itself whenever severe exposure has occurred, because it has been demonstrated that, in those cases where it does not of itself afford protection, it tends to prolong the incubation period and thus allows more time for active immunity to develop."

New Experiments Sponsored by WHO

An important charge on an international health organization is to assist in planning field trials in selected areas which take advantage of experiences from several nations. Two such ventures are now in prospect.

Mass Vaccination of Dogs

Chick embryo vaccine (Flury strain) will be used in Israel where rabies has been on the increase following neglect of regular control measures during the political disturbances. With collaboration of a well-organized veterinary service the demonstration should serve several purposes—giving help where needed, yielding information on vaccination paralysis and duration of immunity under field conditions, and promoting prophylactic immunization of dogs as a method of fighting rabies.

Use of Hyperimmune Serum in Human Beings

The Committee considered the results of experiments in the USA with hyperimmune serum so encouraging that it was thought quite important to foster a large scale trial. In Iran an average of 50 severe wolf bites occur annually, often in series in a single village, and have a case fatality rate of 30% to 50%. Dr. Baltazard, Director of the Institut Pasteur in Teheran, will be in charge of the study. "WHO will provide specialists to check the data on the spot and to assess the results statistically. These results will be published after consideration by the Expert Committee on Rabies at its second session.

"The committee laid down that only cases which report for treatment within 72 hours should be included in the trial. The cases will be divided by strict alternation into two groups, of which one will receive the regular Pasteur treatment alone, while the other will be given serum in addition.

"All other important factors, such as local treatment, which will consist of thorough cleansing with soap solution and no cauterization, have been laid down in detail, and

proper care will be given to equal distribution of all factors which have a recognized bearing on the degree of risk of infection with rabies to which a bitten person is subjected. These are location and severity of bite, interference of clothing and, perhaps, the order in which bites were inflicted, as the saliva might be of diminishing infectivity.

"Provision will be made for the thorough follow-up of cases: patients will be hospitalized for a minimum of two months after termination of treatment; a male nurse will be stationed in the home village; and finally, Dr. Baltazard has undertaken personally to check the patients' health six months after the bite.

"All precautions have also been taken for thorough laboratory studies to be carried out in connexion with this trial. The patients will be bled at regular intervals and the sera tested for immune bodies after shipment to various laboratories in the USA. A close check will also be maintained on the potency of serum and vaccines at the time of their actual use.

"The serum required for this trial will be uniformly prepared from rabbits and is being supplied free of cost by a producing firm in the USA."

Ecologic Studies

In the United States rabies has become more common in some wild animals, notably the fox. This animal has been found infected in other parts of North America and in Eastern Europe. Other animals known to be hosts of rabies are the jackal and wolf in the near East, Southeast Asia and North Africa.

Existence of the disease in wild animals poses a serious problem since even universal control in dogs would not immediately suppress the disease entirely. This should not, of course, diminish attempts to eradicate canine rabies since this is the chief danger to human beings in most of the world.

"The discovery of a form of rabies in Central and South Africa transmitted by vampire bats can be regarded as the most important discovery of our generation on the ecology of the disease. This was the first conclusive demonstration of the existence of asymptomatic carriers. It was shown that vampire bats can harbour rabies virus temporarily in their saliva and remain completely healthy, though some developed the disease and died after prolonged excretion periods. Vaccination with Pasteur 'fixed virus' has given good protection against rabies transmitted by vampire bats."

SPECIAL REVIEWS

JOSEPH STOKES, JR., M.D., *Editor*

CELLULAR COMPOSITION OF THE BONE MARROW IN NORMAL INFANTS AND CHILDREN

By KURT GLASER, M.D.,* LOUIS R. LIMARZI, M.D., AND HENRY G. PONCHER, M.D.
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The purpose of this study is to describe the normal numerical relationship of the cells of the bone marrow at different age levels from birth to adulthood. Publications on this subject are scarce and fragmentary and those available will be reviewed and summarized. In 1944, Osgood and Seaman,[1] after an exhaustive review of the literature, came to the conclusion that before specific recommendations as to normal standards for aspirated marrow could be made, agreement on the technic and nomenclature must be reached.

Most of the articles published on this subject suffer from inaccuracies because of an insufficient number of cases, inadequate distribution by age groups, lack of certainty that the subjects from whom the marrow was obtained were in good health or at least not affected by a disease which could alter the structure of the bone marrow, variations in technic of aspiration, in the preparation of the slide or in the statistical evaluation, and confusion in nomenclature. Criteria for standardization of work on these subjects have been suggested by the above mentioned authors, and we have attempted in this paper to fulfill them sufficiently to make the data of use for comparison with the work of other investigators as well as with individual cases. In the future one may be able to use a more generally accepted nomenclature as at present under preparation by the Committee for Clarification of the Nomenclature of Cells and Diseases of the Blood and Blood-forming Organs.[2,3]

MATERIAL

One hundred fifty-one sternal punctures were performed on normal individuals and blood and bone marrow were studied. Fifty-nine of these individuals were infants below 1 yr. of age, 92 were children and young adults between the ages of 1 yr. and the completion of the 20th yr. of life. The history of each patient was investigated for evidence of illness which could influence the blood or blood-forming organs. The birth histories and prenatal records of infants below 1 mo. of age were investigated with particular care in order to eliminate abnormal cases. All patients used in this study were found to be normal and none had an unusual birth history.

Each patient had a blood study done in order to find signs of pathology not detected by history or physical examination. Five cubic centimeters of blood were withdrawn from a vein immediately preceding or following the marrow aspiration ,and placed in a tube containing a small amount of heparin or ammonium-potassium oxalate mixture (ammonium oxalate 1.2 gm. and potassium oxalate 0.8 gm. dissolved in 100 cc. of distilled water; 0.1 cc. of this mixture was evaporated to dryness and sufficed to prevent the clotting of 1 cc. of blood). The following studies were carried

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TABLE 1

Average Peripheral Blood Values from Birth to 20 Years of Age

Age	Hemoglobin gm./100 ml. blood	Erythrocytes (Mil)	Leukocytes	Hematocrit (erythrocytes) %	Mean corpuscular volume (cu. microns)	Mean corpuscular hemoglobin (micromicrograms)	Mean corpuscular hemoglobin conc. (%)	Sedimentation rate (mm. in 1 hr.)		Reticulocyte count (%)	Icterus index (units)	Stab forms (neutrophils) %	Polymorphonuclear neutrophils (%)	Lymphocytes (%)	Monocytes (%)	Eosinophils (%)	Basophils (%)
								Corrected	Uncorrected								
Days:																	
1st and 2nd	18.4	5.98	22.800	57.3	95.2*	31.4	32.0	4	1.8	6.6	†	15.0	43.6	24.6	11.4	2.0	0.8
3rd and 4th	19.4	6.03	21.680	54.3	91.0	32.4	35.4	8.6	1.8	10.1		19.6	43.0	24.0	6	4.2	0.0
5th and 6th	16.2	5.24	14.940	50.7	96.6	34.6	35.6	10.8	3.4	7.6	41.0	13.6	27.6	40.0	1	4.6	0.2
7th and 8th	17.7	5.95	16.850	53.4	91.0	29.6	30.8	11.6	6.6	4.6	42.0	10.8	26.2	47.4	1	3.6	0.0
11th–14th	16.5	5.21	12.720	50.7	98.2	31.8	32.2	9.0	5.2	0.7	16.5	1.4	29.2	60.0	0	1.4	0.4
15th–17th	14.7	4.33	11.740	44.0	96.3	31.3	32.7	4.7	4.7	‡	10.0	0.0	33.5	54.3	7.8	0.0	0.0
20th–21st	16.0	4.76	12.320	44.3	94.6	31.3	32.7	2	7.3		16.6	1.6	28.0	56.8	11.2	2.5	0.0
22nd–23rd	13.5	4.58	11.420	42.0	91.6	29.0	31.2	1.7	3.0		8.7	1.3	14.3	80.7	2.0	1.7	0.0
25th–30th	12.3	3.95	11.270	35.3	91.3	27.3	30.0	2	12.7		8.3	0.25	28.0	65.5	3.5	2.5	0.0
1st mo.§	16.6	5.18	15.420	55.4	94.1	31.2	32.7	6.8	4.8			8.2	31.2	48.2	8.5	2.6	0.18
Mo.:																	
2nd and 3rd	10.5	3.81	9.930	34.7	91.8	27.3	29.7	6.7	15.1		7.8	8.6	24.0	65.3	5.6	2.6	0.4
4th– 6th	11.3	4.21	13.430	39.7	96.6	26.3	28.3	5.3	10.0		5.8	1.7	35.7	55.7	5.3	2.7	0.7
7th– 9th	10.2	4.66	12.600	35.7	77.0	21.7	28.3	6.0	13.7		6.7	0.3	22.3	70.7	3.3	3.0	0.0
10th–12th	11.2	5.02	16.230	35.1	70.3	22.0	31.0	1.3	15.0		5.8	5.0	2.7	62.7	4.0	0.3	0.3
2nd–12th§	10.7	4.27	12.270	35.9	85.9	25.1	29.4	5.3	13.9		6.9	1.7	26.4	64.0	4.8	2.3	0.4
Yr.:																	
2nd	12.8	4.63	12.570	37.3	80.7	27.7	33.7	0.6	7.0		8.3	1.3	19.0	71.3	6.7	1.0	0.0
3rd and 4th	13.7	5.57	15.850	40.0	72.3	24.7	34.0	8.2	14.8		7.4	1.3	20.8	66.1	6.7	4.7	1.7
5th and 6th	13.1	5.00	9.190	37.7	75.1	25.9	34.4	8.0	16.7		5.7	2.0	30.8	59.8	5.6	1.1	0.9
7th and 8th	12.6	4.52	8.900	38.7	85.3	27.7	32.2	8.1	15.4		5.8	5.0	50.0	34.6	6.3	3.0	0.7
9th and 10th	12.4	4.55	9.130	37.8	83.3	27.0	32.1	5.2	12.3		5.9	3.9	45.2	29.1	6.9	2.7	0.8
11th and 12th	12.9	4.47	7.870	40.8	90.7	28.5	31.3	13.6	18.7		7.2	4.9	47.5	36.8	6.8	3.1	0.8
13th and 14th	13.9	4.78	8.250	41.1	86.1	28.8	33.3	10.9	14.7		6.7	4.1	49.8	37.5	6.7	2.3	0.2
15th and 17th	13.8	4.71	7.510	41.3	87.9	29.0	33.2	10.5	14.0		5.8	6.0	48.1	35.0	7.2	3.0	0.7
17th and 18th	14.1	4.68	8.150	41.7	89.0	30.5	34.0	11.2	14.5		5.8	10.2	50.1	30.0	6.4	2.1	0.7
19th and 20th	14.3	4.71	8.170	41.8	88.1	30.3	33.9	12.2	14.9		6.4	6.0	53.6	27.9	7.5	4.2	0.9
2nd–20th	13.4	4.72	8.999	40.0	84.9	28.5	33.1	9.5	14.8		6.3	4.9	44.8	38.8	6.7	2.8	0.6

* Note should be taken of the high values of the Mean Corpuscular Volume during the 1st 2 wk. of life corresponding to the macrocytosis during this age period. This macrocytosis is better shown by the range of individual values than by average figures: 1st and 2nd day: 82–105 cu. microns; 3rd and 4th day: 70–103; 5th and 6th day: 89–101; 7th and 8th day: 70–99; and 11th to 14th day 94–102. In none of the older children were values above 100 found and only in 2 instances was the Mean Corpuscular Volume 100 cu. microns.

† Average values for the 1st 4 days of life are not recorded because readings above 100 cannot be registered accurately on the equipment used. The estimated average value for the 1st 4 days of life is above 50 units.

‡ Average values are given only for the 1st 2 wk. of life. Because of the rare occurrence of these cells (about 0.5%) after 2 wk. of age, mean values are statistically significant.

§ Mean values for the first month and the age period from 2 to 12 months are recorded separately because of the great physiologic variations of values during these age periods of rapid development. The large number of patients studied during this first year of life, as compared to the more even distribution during the next 19 years of this study period, would make the calculation of the total mean values from birth to 20 years of life statistically insignificant. The effect of age on the blood picture is much greater in the first year of life than in the following 19 years. Thus the mean values given for the 2 to 20 year age groups are statistically more significant.

out: Hemoglobin determination (photocolorimeter), erythrocyte and leukocyte counts in Neubauer counting chambers, differential counts by counting and tabulating 100 white blood cells, red and white hematocrit determinations, sedimentation rate and icterus index by the Wintrobe methods, estimation of the number of platelets, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration. The results of these examinations are summarized in table 1.

Technic

The technic of bone marrow aspiration, staining of slides and counting of cells was the same as described by Dr. L. R. Limarzi.[4-6]

Under aseptic technic the sternum was punctured in or near the midline of the 2nd or 3rd interspace with a 16 gauge University of Illinois Sternal Needle (V. Mueller & Co., Chicago). Procaine was used in older infants and children. The sternum was selected for puncture not only because of its superficial position in the human body but also because it remains a center of hematopoiesis throughout life.[7] The preferred location on the sternum is dictated by the anatomy and development of the sternum.[8] Kato,[9] who studied sterna anatomically, states that at the time of birth the ossification centers of the manubrium, which originally are laid down in pairs, are fused into one. The next 3 segments (sternebrae) show pairs of ossification centers which in many instances (20%)[7] have not been fused at birth. Ossification and fusion of these centers begins at the cephalic end of the sternum and proceeds downward. At about 8 to 10 yr. of age ossification centers have filled the sternebrae almost completely. For the above reasons, the preferred site of puncture in infants is at the level of the second interspace, somewhat off the midline. One might attempt to draw the marrow fluid from the spongiosa center in the manubrium,[7] but this center is very thin and perforation of the sternum is more likely to occur. Because of its central location, however, it is usually the easiest found in the infant below 1 mo. of age and therefore often selected. The thickness of the sternum at the 2nd interspace varies from 2 mm. in the newborn infant to 10 mm. or more in the adult. The anterior lamina, which has to be perforated before the spongiosa is reached, is between 0.5 and 2 mm. thick. The knowledge of these facts is particularly important if one engages in sternal punctures in infants in whom the anterior lamina is still cartilaginous and a sudden give upon its perforation is therefore not felt.

After piercing the skin at an acute angle the needle was forced through the anterior plate of the sternum at a right angle until the sudden absence of resistance or the distance covered by the needle point indicated that the needle had reached the marrow cavity. With a 5 or 10 cc. syringe 1 cc. of marrow fluid was withdrawn—a smaller amount had to suffice in small infants (see below)—and placed in a paraffin-lined tube containing a very small amount of powdered heparin. The heparin and bone marrow were mixed by inverting the tube several times; then the contents were pipetted into a Wintrobe hematocrit tube and centrifuged for 5 min. at 2000 rotations/min. Fat, plasma, myeloid-erythroid cells and mature red blood cells were separated by this method. The height of the various layers was recorded. There were variations with the age of the individuals in the thickness of the different layers but the interpretation of the significance of these variations must be left to some special investigation in this field.

The data available for the various age groups—in subdivisions similar to those used throughout this paper—were recorded in table 2. In some cases only smears were made due to lack of sufficient amount of marrow fluid for quantitative (volumetric) studies. On inspection one finds the top layer of fat, followed by the plasma layer, the myeloid-erythroid (buffy) layer and the layer of the mature red cells. The myeloid-erythroid layer is small during the 1st yr. of life and higher and more constant during the following years. The fat layer, too, seems to increase with the age of the child. In the group below 1 yr. many tubes show no visible layer of fat or only a trace, whereas in the older age periods the fat layer is almost always present in a measurable amount. The mature erythrocyte layer shows a decrease during the first days of life, while the plasma layer does not show any definite age-conditioned variations. A possible explanation for these findings may be seen in the anatomy of the marrow cavity and the histologic composition of the marrow. The larger cavity of the older individual permits the aspiration of a purer marrow with less dilution with peripheral blood, which explains the higher myeloid-erythroid layer in the older group. The higher fat content of the marrow in older individuals may be the explanation for the increased amount of fat found in these specimens.

After recording the height of the layers, the fat and most of the plasma were removed and the myeloid-erythroid layer with a small amount of plasma was pipetted on to a paraffin-lined watch glass and mixed. Smears were made from this material in the following manner: A drop of marrow fluid was placed on a microslide and a second slide applied at an angle of 30 to 45 degrees. After permitting the drop of fluid to spread in the angle formed by the 2 slides the top slide was moved over the horizontal slide, effecting the spread of the marrow fluid. The same process was carried out with a drop of blood obtained from finger tip or ear lobe of the child.

After the slide had been dried in air, Wright stain was applied for 1½ to 3 min., then diluted

TABLE 2

VOLUMETRIC FINDINGS OF BONE MARROW FROM BIRTH TO 20 YEARS (PERCENTAGES)

Age Period	Total No. of Cases	Fat		Plasma		Myeloid-Erythroid Layer		Red Blood Cell Layer		Total Cell Count (in thousands)	
		Aver.	Range	Aver.	Range	Aver.	Range	Aver.	Range	Aver.	Range
Days:											
1st and 2nd	5	0.0		44.0	36.0–54.0	5.4	4.0– 7.0	50.6	40.0–60.0	389	135–600
3rd and 4th	5	0.0		45.5	36.0–66.0	5.8	3.0– 8.0	48.0	28.0–58.0	366	230–475
5th and 6th	5	0.0		43.25	28.0–52.0	6.2	4.0– 8.0	44.4	20.0–64.0	348	230–430
7th and 8th	5	0.0		61.0	40.0–76.0	6.9	4.5–10.0	32.0	16.0–50.0	427	230–590
13th	2	0.0		38.5	34.0–43.0	6.5	6.0– 7.0	55.0	50.0–60.0	547	435–660
20th–22nd	4	0.6	0.0–1.0	48.1	25.0–63.5	6.6	5.0– 9.0	44.6	29.5–66.0	418	375–475
Mo.:											
2nd–12th	16	0.11	0.0–1.0	64.0	60.0–71.0	4.9	1.0–10.0	22.4	9.0–34.0	405	165–560
Yr.:											
2nd	3	0.33	0.0–1.0	68.67	56.0–81.0	5.33	4.0– 7.0	25.67	12.0–40.0	410	390–430
3rd and 4th	6	0.92	0.5–1.0	50.25	45.0–59.0	9.5	7.0–15.0	39.0	30.0–44.0	448	255–550
5th and 6th	8	0.94	0.0–2.0	53.1	49.5–61.0	8.9	5.0–15.0	36.9	28.0–45.0	468	285–955
7th and 8th	15	1.2	0.0–3.0	48.5	39.0–62.0	11.5	4.0–20.0	38.8	31.0–47.0	464	250–725
9th and 10th	9	1.78	1.0–3.0	51.0	47.0–54.0	10.55	5.0–22.0	37.0	30.0–46.0	483	255–700
11th and 12th	9	2.67	1.0–6.0	48.2	40.0–54.0	11.33	5.0–18.0	38.33	34.0–45.0	451	215–825
13th and 14th	9	2.28	0.5–8.0	47.83	40.0–57.0	10.0	7.0–13.0	39.89	34.0–48.0	402	305–485
15th and 16th	13	1.6	1.0–3.0	48.87	37.0–64.0	8.54	4.5–15.0	40.6	29.0–50.0	396	195–890
17th and 18th	10	2.3	1.0–5.0	49.2	39.0–60.0	6.8	4.0–10.0	41.6	36.0–52.0	323	165–390
19th and 20th	10	2.2	1.0–6.0	49.35	37.0–58.0	7.55	2.5–11.0	40.9	35.0–54.0	337	90–550
2nd–20th	92	1.02	0.0–8.0	50.04	37.0–81.0	9.32	2.5–22.0	38.89	12.0–54.0	419	90–955

The number of cases shown on this table is smaller than the total number of cases reported in the differential counts because in some patients the amount of marrow withdrawn was not sufficient to permit volumetric determinations.

with distilled water, mixed and allowed to stand for 15 to 20 min., after which period the slide was washed with distilled water and air dried. For the blood slide the same stain was used but the fixation period with the concentrated Wright stain was 3 min. and the staining period 7 min.

When the slides were thus prepared they were ready for examination under oil immersion.

STATISTICAL METHODS AND SOURCES OF ERROR

On each of the slides, 400 nucleated (500 on some slides) were counted and recorded. The numbers of cells and cell groups of all cases as well as of smaller groups of cases, arranged by age, were then tabulated and statistically evaluated by determining the mean (average), standard deviation,* frequency distribution* and range. The findings were

* The data marked with an asterisk (*) are presented in this study only for the main groups (total erythroid and myeloid series and lymphocytes). The median, standard deviation, frequency distribution and graphic description of the individual cells have been reported in detail by one of the authors (K.G.).[10]

presented graphically* or in table form, whichever way appeared more descriptive. Observations on the percentile relationship of the different cells in the same patient-age-group and of the same cells in different patient-age-groups were investigated. The findings were compared, as far as possible, with the results obtained and published by other investigators.

The above described methods of puncture, preparation of slides and statistical evaluation offered opportunity for certain errors and misinterpretations, which we wish to mention here, not only to document their awareness of these shortcomings but also to help understand the great variations within our findings and the discrepancies in other reports, to caution workers in this field against too great reliance upon single findings and to stimulate future work which might further eliminate these sources of error.

An uneven distribution of cases would lead to erroneous conclusions; in order to avoid errors on this basis the statistical grouping of the cases in this study was not done on an arbitrary basis but directed by the following considerations: The total average count of the individual cells or cell groups was obtained by adding the figures of all cases above one year of age. There were three reasons for omitting cases below one year of age from the calculation of the total average: 1. There were 59 cases in this series below one year of age as compared to 92 for the following 19 years; this would weight the results heavily toward the first year of life and not produce a true average of the group. 2. These findings and the findings of other investigators showed that most variations in number occurred during the first year and—still more markedly—during the first month of life. 3. The neonatal adjustments do not seem to be completed until the end of the first year of life. Figures on this very variable period would not only alter the average unjustifiably, but the varying values for the first year which are most interesting and important would disappear in the large total number if all age groups should be considered together.

For the same reason the first month of life was considered and evaluated separately. During this period the variations were most striking and by their consistency of occurrence proved that they were not accidental. Statistically, too, there was a reason for separating the first month from the first year of life because there were 42 patients of less than one month of age and only 17 between the first and twelfth months. Again the data for the first month of life would have unduly influenced the figures for the total year. It was therefore considered more correct to obtain average values for the first year by considering the last 11 months and to analyse the first month separately. As will be seen in the graphs and tables, this first month of life is the time when characteristic changes occur and the above method of grouping and subdividing has permitted the authors to demonstrate these features of the numerical relationship of the various cells at different age levels of the individual.

In the following text the group of 42 cases from birth to one month of age will be referred to as Age Group I, the group of 17 cases from one month to one year of age as Age Group II and the group of 92 cases from one to 19 years of age (including the twentieth year) as Age Group III.

By expressing the numbers of cells in percentages rather than in absolute figures per volume unit of marrow fluid, the findings are less influenced by the differences in dilution which seem to be an unavoidable source of error by any method of aspiration. Variations

* See footnote on preceding page.

in dilution of bone marrow with peripheral blood will alter the findings, the degree of dilution being influenced by the amount of marrow withdrawn, the size of the cavity from which it is withdrawn, and the proximity of blood sinuses to the needle point. It is also important to consider which part of the specimen is used (as, for instance, the first drop in the needle, as used by Segerdahl,[11,12] would be the last drop withdrawn and therefore contain more dilution material than the blood in the syringe). The variability of the dilution factor was minimized by standardizing the amount of marrow fluid withdrawn, by thoroughly mixing the specimen and by centrifuging the material and then preparing the film from the buffy layer which contains mainly the nucleated cells.

Greif,[13] Segerdahl[11,12] and Vogel, Erf and Rosenthal[14] made comparative studies on the number of total nucleated cells on slides obtained from the first and last part of a large specimen and found considerable differences in numbers. Osgood and Seaman[1] in their table for tentatively recommended standards gave the average values for two methods of aspiration as 35,000 cells if 0.5-10.0 cc. were aspirated, and 75,000 cells if 0.05-0.5 cc. were aspirated.

Because of these notable variations these authors recommended standardization of the amount of fluid withdrawn. This was attempted in the method recommended by Limarzi[4-6] which was used throughout this study. This approach, too, can be questioned as to its accuracy because different sizes of the marrow cavity from which the marrow is withdrawn will cause variations in the degree of dilution. It seems, therefore, that if the amount withdrawn would be reduced to a minimum—0.1-0.2 cc. (Arinkin[15])—the dilution would be minimal and only slightly affected by the size of the marrow cavity. In using this method, however, one has to consider variations produced by the location of the needle point with regard to the nearest blood sinus. Furthermore this technic would not permit thorough mixing and concentration of the specimen, and the small specimen size would prevent accurate measurement and standardization of the amount withdrawn.

Another disadvantage to the method of withdrawing 1 cc. or even larger amounts was encountered when the marrow cavity was very small, as in young infants or in cases of individual variations of the sternal anatomy in older children. In these cases the "standard amount" of aspiration fluid would be obtained only by drawing a larger or smaller amount of peripheral blood into the cavity and thus obtaining varying degrees of marrow-blood mixtures. In some instances, particularly in smaller children, it was impossible to obtain 1 cc. of fluid and smaller amounts of marrow had to suffice for centrifugation and preparation of the slide. This was a further handicap to standardization but did not necessarily interfere with the accuracy, as the withdrawal of a smaller amount from a smaller cavity would lead to less dilution than the withdrawal of a larger amount. To use smaller amounts in certain cases might therefore actually increase the accuracy by equalizing the dilution of the bone marrow, but would prevent standardization. Finally, in some very small infants the quantity of marrow obtained was so small that centrifugation was impossible and direct smears were made. This, however, was necessary in very few cases only.

Admixture of blood does not only lower the total nucleated cell count but also, to a somewhat lesser degree, alters the differential count. If dilution takes place the nucleated cells which occur in large number in the blood, such as polymorphonuclear neutrophils and lymphocytes, would be more frequent in the marrow preparation. Since the cells are reported in percentages, the remaining cells would appear proportionately lower. Throughout this study we have not, however, noted that this difference was significant enough

to devaluate differential counts materially. Here again one must consider the great variations within individual counts done on the same patient, conditioned by uneven distribution of cells on the slide and emphasized by the relatively low total number of cells counted (400). In comparison to these variations the influence of the dilution upon the percentages of cells seems to be small. These considerations are therefore more of a theoretic than practical nature.

Cell Definition, Classification and Nomenclature

One of the difficulties which many investigators mention and which we have also encountered is the confusion which reigns in the field of classification, definition and nomenclature. Because of the maze of names and categories it was found necessary to give the definition, classification and nomenclature of the cells as used in this study, so that others, not familiar with these methods, may find it possible to compare our findings with their own and those of others. To further clarify the terminology, photomicrographs of cells which might give cause for misinterpretation are included (Figs. 1-8). For the cells which were not photographed the descriptions in Atlases of hematology[16,17] were used.

The pronormoblasts (Fig. 1) are the youngest cells of the erythroid series and vary in size from 12 to 15 micra or larger. Their nucleus is surrounded by a small amount of strongly basophilic cytoplasm without granules or hemoglobin. The nucleus itself is round, with coarse, clumpy, pyknotic chromatin, particularly as compared to the nucleus of the myeloblast which has a finer chromatin structure. The nucleus is not as transparent as that of the myeloblast, and nucleoli are present but not as well visible as in the myeloblast. Chromatin and parachromatin are well differentiated. The nucleus of the lymphocytes is more pyknotic, the differentiation between chromatin and parachromatin is not sharp and there is only a thin rim of cytoplasm around the nucleus.

In the literature the terms macroblast, proerythroblast, erythroblast, "erythrogonie," normohemoblast and lymphoidocyte are used for this cell.[9,18-23] The term megaloblast is used[11,12,14,16,24-31] by some to describe this type of cell, although others include in this group cells which according to Jones[32] occur only in pathologic bone marrow of pernicious anemia and nutritional anemia in infants.

The size of the normoblasts (basophilic, polychromatic, orthochromatic) (Figs. 2, 3 and 6) varies from 8 to 12 micra. The cytoplasm has no granules, except for some rod-shaped mitochondria particularly well visible with supravital stain. The color varies with the age of the cell from basophilic blue to acidophilic red with a muddy gray intermediary stage. The nucleus becomes progressively more pyknotic, and clumps of chromatin with clearly and sharply defined parachromatin are visible. The chromatin may be in wheel-spoke or checker-board arrangement. In differentiation, lymphocytes have only a thin rim of cytoplasm around the nucleus, which is pyknotic and more homogenous, and their parachromatin and chromatin are not sharply differentiated. Pronormoblasts show nucleoli, a less pyknotic nucleus, and a more basophilic cytoplasm.

As the change in color in the cytoplasm occurs gradually, the separation into the three groups (basophilic, polychromatic, orthochromatic) is somewhat arbitrary. For this reason the statistical evaluation is more accurate and more comparable to others if the subgroups of the normoblasts are considered together. The individual interpretation of the examiner, the momentary condition of his lighting facilities and the conditions of his eyes may influence the classification of the cells. A comparison between several reports

is therefore more likely to correspond if the subgrouping is omitted and the normoblastic group considered in total.

The terms macroblast, erythroblast and megaloblast are used in the literature for this cell group.[9,11,12,14,18-23,27-29,33]

The myeloblasts (Fig. 4) range in size from 10 to 20 micra. There is a small amount

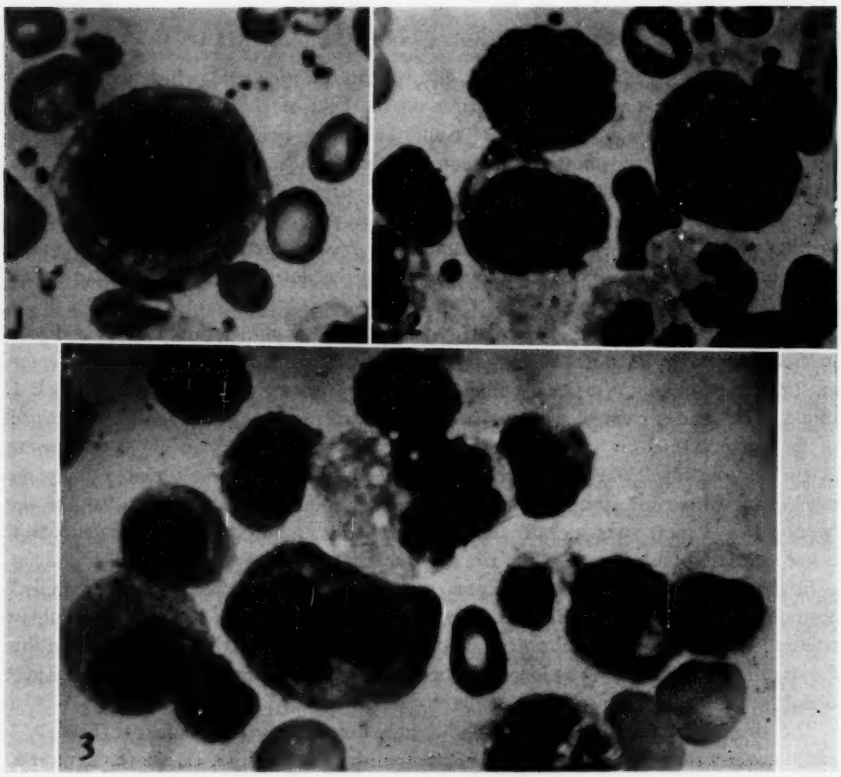

FIG. 1. Pronormoblast.
FIG. 2. Basophilic normoblasts.
FIG. 3. Erythroid cell in mitosis surrounded by number of polychromatic normoblasts. Note lymphocyte.

of intensely basophilic cytoplasm witn no specific but occasionally azurophilic granules. The nucleus is round or oval, rarely slightly indented or lobulated. The chromatin structure consists of thin, fine strains in netlike fashion, with a sharp distinction between chromatin and parachromatin. One to several light blue nucleoli are found. In differentiating this cell from others, the leukoblast shows a cytoplasm with many large azurophilic granules, whereas the cytoplasm of the pronormoblast never shows granules. The nucleus of the latter cell is never lobulated or indented and the chromatin structure is coarser and more pyknotic. The nucleoli of the pronormoblast are not well visible.

Without wanting to take issue with the various theories of cell genesis, this cell group

was classified and counted among the myeloid series. Its small number of occurrence would, however, not influence materially the numerical relationship of any group. The terms lymphoidocyte and hemocytoblast are used by others for this cell group.[19, 30, 34]

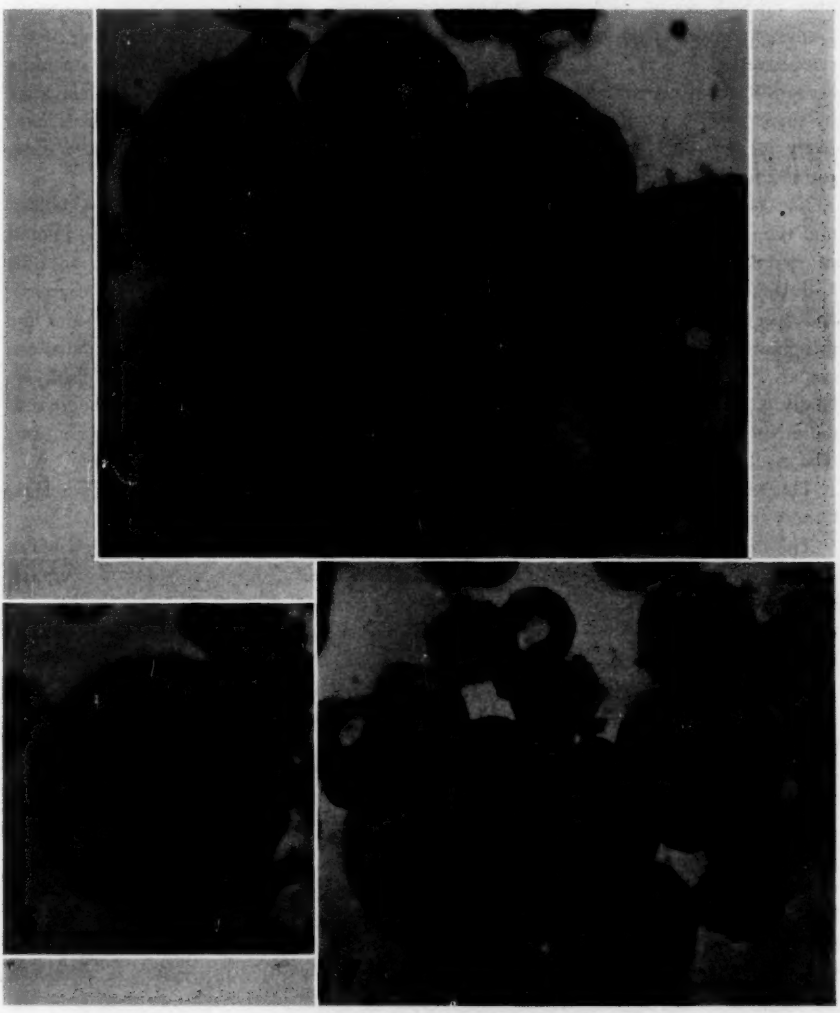

FIG. 4. Myeloblast and leukoblasts.
FIG. 5. Promyelocyte.
FIG. 6. See page 799.
FIG. 7. Myeloid cell in mitosis.

The developmental position of the leukoblasts (Fig. 4) is considered between the myeloblasts and the promyelocytes. Depending on the theory of cell development, this would be the youngest or second youngest cell of the myeloid series. They vary in size

from 10 to 15 micra. Their cytoplasm is basophilic with many large azurophilic round granules, and the nucleus is round or slightly indented or lobulated. The chromatin structure is fine, yet somewhat coarser than in the myeloblast. There are several light blue nucleoli visible. In contrast, the promyelocytes show the beginning of specific granulation, particularly in a Hof-like indentation of the nucleus with a clearing of the cytoplasm in this area, producing a "sunburst effect." The myeloblasts show an intensely basophilic cytoplasm with no or very few small azurophilic granules. This cell is classified by some[16, 24, 25, 35] as myelocyte A or B. Others who do not use the term leukoblast most likely include the younger forms of this group among the myeloblasts and the older forms among the promyelocytes.

The promyelocytes (Fig. 5) have their developmental place between the leukoblasts and the myelocytes. They measure between 10 and 15 micra and have a larger amount of cytoplasm than the younger forms of the myeloid series. It is generally basophilic with some areas of acidophilia. The large azurophilic granules are becoming less frequent and specific granules appear in a Hof-like indentation of the nucleus. In this area the cytoplasm is clearer, producing a "sunburst effect." Minor indentations and lobulations are always present in the nucleus and its chromatin structure is coarser. Nucleoli are barely or not at all visible. In differentiation, the leukoblasts have a smaller amount and more basophilic cytoplasm with more azurophilic granules, and nucleoli are always visible. The myelocytes, in turn, have acidophilic cytoplasm and no azurophilic granules.

This term is used by most authors, although some include in this group our leukoblasts. Others call this cell immature (halbreifer) myelocyte.[18,22,33]

The myelocytes (Figs. 6 and 8) range in size from 10 to 15 micra. Their cytoplasm is oxyphilic, with no or very few azurophilic granules and many mature specific granules, easily recognized as neutrophilic, eosinophilic or basophilic. The nucleus is denser and smaller than in the younger forms of this series, and shows the beginning of kidney-shaping. No nucleoli are seen.

The definition and classification of the myelocyte offer in our opinion some difficulty, since some of the more mature forms of myelocytes can easily be placed among the next higher developmental stage, the metamyelocytes. Some authors use the terms myelocyte C or semi-mature or mature myelocyte.[18,24,25,33,35]

The metamyelocytes (Fig. 8) vary in size from 10 to 15 micra or smaller. Their cytoplasm is oxyphilic and contains only mature specific granules. The nucleus is more pyknotic, elongated and strongly kidney-shaped. The indentation produces a curved nucleus whose thickness is equal throughout or narrower at the point of indentation. The constriction never reaches the point at which lobulation is observed.

This cell group stands developmentally between the myelocytes and polymorphonuclears. Some authors[9, 11, 12, 20, 27, 28, 31, 33] subgroup these cells and place the staff forms between the metamyelocytes and the polymorphonuclear cells. The differentiation is made by the more slender appearance of the nucleus in the staff forms with a more pronounced pyknosis. The cytoplasm in the metamyelocytes may have a slight bluish tinge if compared with the staff forms, according to Veeneklaas[27, 28] and Segerdahl.[11, 12] The names metamyelocytes, nonsegmented cells and juvenile forms are used by some investigators interchangeably.

The polymorphonuclear cells (Fig. 6) constitute the most mature cells of the myeloid series. Their size varies from 10 to 15 micra. The cytoplasm is always completely oxyphilic and only specific and mature granules are seen. The nucleus is segmented, having only

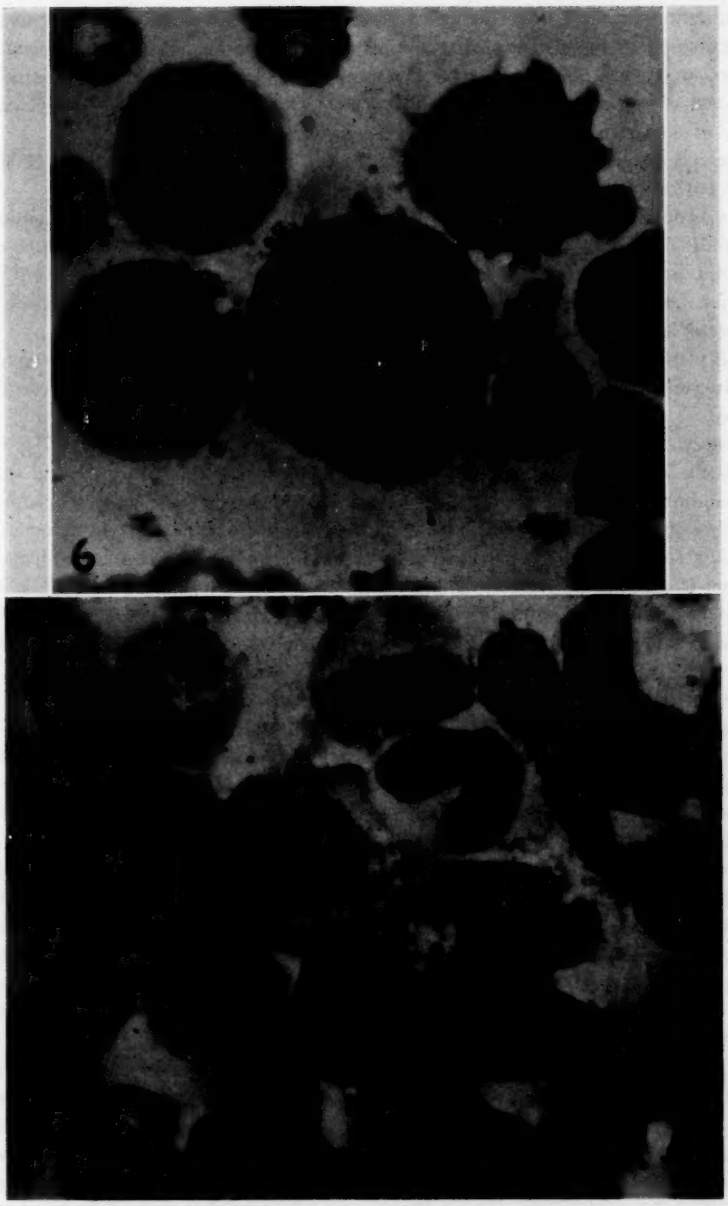

FIG. 6. Plasma cell, basophilic normoblast, neutrophilic myelocyte and polymorphonuclear.
FIG. 8. Myeloid cells in various phases of development, mostly myelocytes and metamyelocytes.

hair-like connections between segments (lobes). The number of segments is considered an indication of the age of the cell (Arneth[36]). There is generally no controversy in differentiating these cells, except that injured metamyelocytes may appear polymorphonuclear, or folded polymorphonuclears may appear like metamyelocytes. The cells are described as segmented neutrophils, polymorphonuclears, granulocytes or lobocytes. There seems to be no controversy as to their definition and classification.

The specific granules of the cells just described of the myeloid series may be neutrophilic, eosinophilic or basophilic, depending on their chemical composition.

The lymphocytes (Fig. 3) measure from 8 to 10 micra and have a small amount of basophilic cytoplasm with occasional azurophilic granules. The nucleus is small, round, pyknotic, nontransparent and in the center of the cytoplasm. There is no sharp differentiation between chromatin and parachromatin. The normoblasts, in comparison, have more cytoplasm and sharply outlined chromatin parachromatin structure.

The plasma cells (Fig. 6) are somewhat larger (10 to 15 micra), and resemble the lymphocytes in structure of cytoplasm and nucleus except that the latter is eccentrically situated.

Monocytes, measuring from 12 to 20 micra, have an abundant amount of grey-blue cytoplasm. The color is not an even blue but has a sprinkled appearance. Several vacuoles and azurophilic granules are usually present. The nucleus is large, indented, kidney-to-horseshoe-shaped, with fine reticulated chromatin. There are no nucleoli. In differentiation, the blast forms of other cells have an even blue cytoplasm, a more strain-like rather than net-like chromatin structure, and nucleoli.

The reticulo-endothelial cells are large and vary greatly in size. The cytoplasm is abundant and pale-basophilic without sharp cell boundary. Phagocytosis as seen by the presence of cell fragments and vacuoles within the cytoplasm is a characteristic of these cells. The nucleus is eccentrically situated, large in size, with light thin strains of chromatin and some nucleoli. The following names are frequently used for these cells: mononuclear phagocytes, endothelial phagocytes, clasmatocytes, reticulum cells, macrophages and histiocytes.

Megakaryocytes measure up to 60 micra. Their cytoplasm is blue to purple with many azurophilic granules. The cells are not sharply outlined and sometimes have several pseudopodes. The nucleus is dense, jelly-like, homogenous and sometimes lobulated.

Hematogones resemble lymphocytes in their structure, but are smaller and show only occasionally a thin rim of cytoplasm. Their nature is still very much under discussion. Naegeli[18] believes they may be the stem cell of the red and white series, Vogel et al.[14, 29] call it the mystery cell of the bone marrow. They may in many cases be only detached nuclei of injured cells. Their significance and classification are not known. Statistically they are insignificant and are not included in the figures of this paper.

Megaloblasts vary in size from 15 to 25 micra. The amount of cytoplasm is larger than in the normoblasts and the nucleus has sharply defined, thin strains of chromatin; no clumping is present as seen in normoblasts. These cells, as described and discussed by Jones in *Downey's Handbook of Hematology,*[32] are not considered part of the normal bone marrow picture. Many authors, however, use this term for cells not fitting the description of Jones but rather as part of the normoblastic series.

Hemohistioblasts (Ferrata cells) are probably artefacts (Naegeli,[18] Segerdahl,[11, 12] Maximow,[34] Schulten[23]) and may be smudged cells of the myeloid series. It is possible

that some reticulo-endothelial cells are included among them as their description resembles the description of these cells.

Although the preceding terms are used throughout this publication it might be well to mention the new terms as recommended by the Committee for Clarification of the Nomenclature of Cells:[2,3]

Terms Used in This Publication	New Terms Suggested
Erythroid Series	*Erythrocytic Series*
Pronormoblast	Rubriblast
Basophilic Normoblast	Prorubricyte
Polychromatic Normoblast	Rubricyte
Orthochromatic Normoblast	Metarubricyte
Myeloid Series	*Granulocytic Series*
Myeloblast	Myeloblast
Leukoblast & Promyelocyte	Progranulocyte
Myelocyte	Myelocyte
Metamyelocyte	Metamyelocyte & band cell
Polymorphonuclear cell	Segmented
Plasma Cell	Plasmacyte

Erythroid Series

The cells of the erythroid series in this study include the pronormoblasts and the normoblasts, the latter being subdivided into basophilic, polychromatic and orthochromatic normoblasts. The individual counts and averages are demonstrated graphically (charts 1 and 2) and the data summarized also in table form (tables 3 and 4).

The pronormoblasts, the youngest cells of the erythroid series, occur in the smallest number. The average for Age Group I (the first month of life) is 0.78% (range 0.0-2.75%), for Age Group II (the first year of life with the exclusion of the first month) it is 0.59% (range 0.0-1.5%) and for Age Group III (from the end of the first to the end of the twentieth year) it is 0.47% (range 0.0-1.5%). Thus it seems that the younger the patient the higher the number of pronormoblasts, an observation which appears logical as we do expect to find the immature forms of the cells to decrease in frequency with advancing age (Kato[9]). Statistically these cells are of little importance due to their low incidence (on some counts of four hundred cells no pronormoblasts were encountered). Their seemingly higher number during the first month of life and particularly during the first days probably indicates the greater bone marrow activity which was described by Büngeler and Schwartz[37] as blood crisis due to birth trauma. These authors found the number of immature cell forms increased in the blood of the newborn infant, particularly following prolonged labor and difficult delivery.

The basophilic normoblasts, which occur in higher number, are somewhat easier to evaluate and their findings are therefore less dependent upon statistical errors. Their variations by age parallel the course of the total erythroid series, although the wide ranges might make the average figures less significant. The average percentage for Age Group I is 1.88% (range 0.0-6.75%), for Age Group II 2.08% (range 0.25-4.25%) and for Age Group III 1.69% (range 0.25-4.8%). Most of the reports in the literature do not make separate listings on the number of cells found in this group.

Let us leave the polychromatic normoblasts for the last, because of their numerical importance, and consider next the orthochromatic normoblasts, which are developmentally the most mature group of nucleated cells in the erythroid series. Like the basophilic normoblasts, they occur in small number and are of little statistical significance. Their

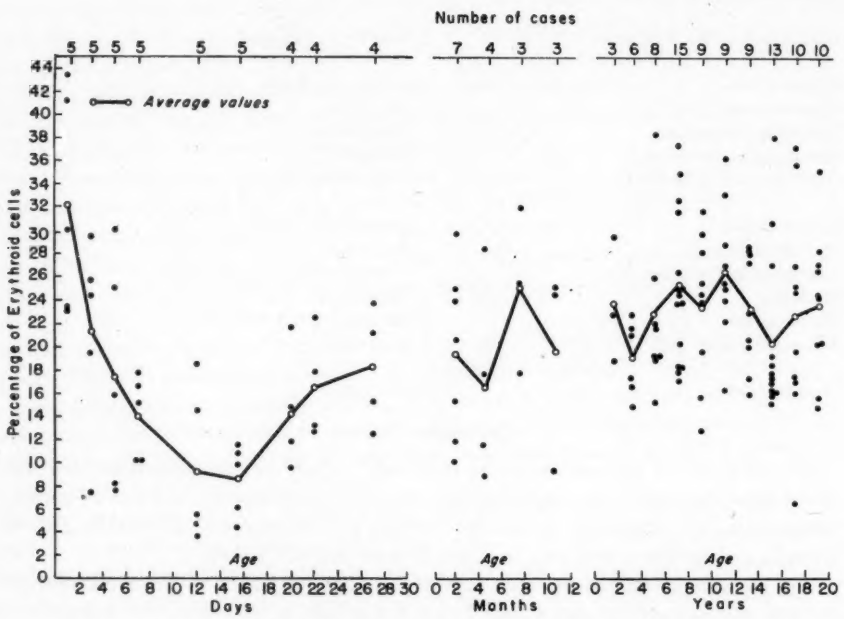

CHART 1. Scattergram and average values of erythroid series.

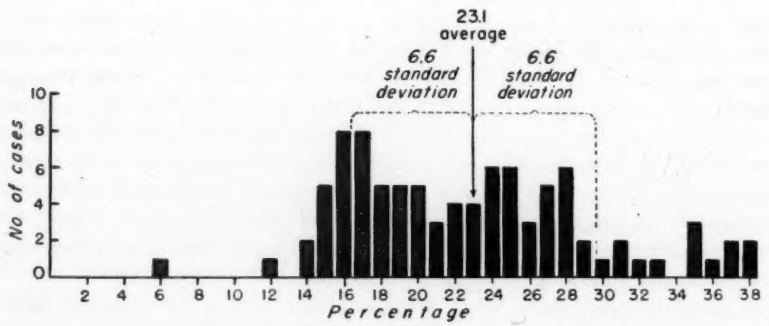

CHART 2. Frequency distribution and standard deviation of erythroid series.

average value for Age Group I is 1.57% (range 0.0-4.75%), Age Group II 2.53% (range 0.0-8.5%) and Age Group III 2.72% (range 0.0-7.75%). In comparing these figures with those of the total erythroid series we find that due to the low number of orthochromatic normoblasts the trend is not as noticeable as it is with the polychromatic normoblasts which are represented in larger number.

TABLE 3

DIFFERENTIAL BONE MARROW COUNTS BY AGE GROUPS

Age	Cells of Myeloid Series (Neutrophils) — Average Values (Percentages)							Cells of Erythroid Series — Average Values (Percentages)					Myeloid-Erythroid Ratio	Average Values (Percentages)
								Normoblasts						
	Myeloblasts	Leukoblasts	Promyelocytes	Myelocytes	Metamyelocytes	Polymorphonucl. cells	Myeloid Series	Pronormoblasts	Basophilic	Polychromatic	Orthochromatic	Erythroid Series		Lymphocytes
Days:														
1st and 2nd	0.8	1.64	3.7	16.35	20.3	6.65	53.82	0.75	2.65	27.05	1.64	32.2	1.85	13.5
3rd and 4th	0.6	1.7	6.45	18.35	28.45	12.65	70.90	0.25	1.95	18.05	1.15	21.2	4.54	7.75
5th and 6th	1.8	1.95	6.80	17.5	31.15	6.10	66.95	0.90	1.85	13.70	0.8	17.25	5.45	13.10
7th and 8th	2.0	2.01	2.84	17.33	35.12	7.56	72.91	0.80	1.16	10.39	1.54	13.85	5.60	12.84
11th–14th	1.3	1.35	1.3	18.05	26.95	15.8	68.05	0.8	1.3	5.45	1.6	9.15	11.18	22.55
15th–17th	2.55	2.45	2.3	19.75	24.60	11.0	65.55	0.8	1.05	4.9	1.65	8.40	9.36	25.35
20th and 21st	2.0	2.31	3.62	9.62	14.25	8.81	45.37	1.19	1.69	10.5	0.94	14.31	3.44	40.0
22nd and 23rd	1.81	2.12	4.25	13.19	17.62	5.69	48.12	1.06	3.12	10.0	2.31	16.50	3.11	35.19
25th–30th	2.19	1.25	2.44	19.56	29.19	8.81	68.0	0.56	2.5	12.31	2.81	18.19	4.08	13.19
1st mo.	1.65	1.86	3.77	18.14	25.64	9.33	62.78	0.78	1.88	12.59	1.57	16.82	5.53	19.74
Mo.:														
2nd and 3rd	2.48	0.94	0.43	16.59	21.56	6.32	50.38	0.64	2.1	13.40	3.26	19.48	3.13	29.43
4th– 6th	1.56	1.62	0.56	16.31	27.81	8.62	59.25	0.62	2.75	12.25	0.75	16.62	4.60	24.0
7th– 9th	1.83	0.75	1.08	15.83	23.67	6.8	53.7	0.50	1.92	18.17	4.33	24.91	2.35	21.25
10th–12th	1.17	1.17	1.0	18.5	24.5	8.0	57.92	0.50	1.33	16.33	1.42	19.58	3.98	21.92
2nd–12th	1.92	1.11	0.68	16.73	23.92	7.25	54.38	0.59	2.08	14.49	2.53	19.78	3.49	25.38
Yr.:														
2nd	0.67	1.67	1.75	13.33	21.75	14.08	56.33	0.83	1.25	19.5	2.08	23.66	2.48	19.33
3rd and 4th	1.39	0.81	2.4	15.93	21.96	16.44	62.95	0.45	0.97	16.37	1.17	18.97	3.41	18.64
5th and 6th	1.76	1.5	1.75	17.16	22.88	12.65	59.28	0.46	1.22	17.3	3.55	22.53	2.85	17.52
7th and 8th	0.96	1.53	2.1	17.35	23.43	12.29	61.02	0.40	1.74	19.38	3.35	25.14	2.64	13.55
9th and 10th	1.44	1.68	2.23	16.47	26.14	10.86	62.62	0.32	1.63	19.11	2.36	23.48	2.94	13.6
11th and 12th	1.12	1.49	1.94	15.31	22.18	12.19	57.81	0.20	1.80	21.78	2.67	26.5	2.32	16.02
13th and 14th	1.18	0.76	1.52	16.37	21.58	12.25	58.39	0.45	1.31	18.28	3.12	23.18	2.68	17.98
15th and 16th	1.29	1.72	2.03	16.76	23.25	13.26	62.10	0.54	2.16	15.1	2.52	20.33	3.34	17.41
17th and 18th	1.41	1.89	1.5	15.98	22.88	13.89	59.87	0.63	2.18	17.05	2.24	22.59	3.65	16.05
19th and 20th	1.02	1.09	0.75	17.0	24.98	13.34	62.30	0.66	1.72	18.84	3.02	23.64	2.89	14.59
2nd–20th	1.23	1.44	1.8	16.46	23.27	12.92	60.59	0.47	1.69	18.2	2.72	23.12	2.94	16.03

Figures for the eosinophils and basophils, because of their low incidence, are indicated in the text only and omitted in this table, therefore the figures listed for the individual cells of the myeloid series do not add up to the figures given for the total myeloid series.

At this point we might mention again that the differentiation of orthochromatic and polychromatic cells is rather arbitrary and, as discussed previously, is dependent upon the amount of hemoglobin in the cytoplasm and its resulting color variation. It is therefore possible and even probable that a number of orthochromatic cells were placed within the polychromatic group or vice versa. Consideration must also be given to some other sources of error, which fortunately did not enter this study, such as differences in staining methods and technic as well as the counting of the cells being done by different

TABLE 4

SUMMARY OF DIFFERENTIAL BONE MARROW STUDIES ON 92 CASES
1–20 YEARS OF AGE

Cells	Percentage: Range	Average
Myeloid Series:		
Myeloblasts	0.0 – 3.25	1.23
Leukoblasts	0.0 – 4.0	1.44
Neutrophils		
Promyelocytes	0.0 – 4.5	1.8
Myelocytes	8.5 –25.25	16.46
Metamyelocytes	14.0 –34.25	23.27
Polymorphonuclear Cells	4.5 –29.0	12.9
Eosinophils (all stages)	1.0 – 9.0	3.58
Basophils (all stages)	0.0 – 0.75	0.06
Total Myeloid Series	45.0 –77.0	60.59
Erythroid Series:		
Pronormoblasts	0.0 – 1.5	0.47
Basophil Normoblasts	0.25– 4.8	1.69
Polychromatic Normoblasts	4.8 –34.0	18.2
Orthochromatic Normoblasts	0.0 – 7.75	2.72
Total Erythroid Series	6.4*–38.25	23.12
Myeloid-Erythroid Ratio	1.22–11.78†	2.94
Lymphocytes	4.75–35.75	16.03

* Next figure above 6.4 is 12.75.
† Next figure below 11.78 is 5.22.

observers, which might further alter the findings. In this study all stainings were done by one technician and all cell counts by one of us. From a statistical point of view the variation in the method of classification of the orthochromatic series would not materially influence the figures for the total nucleated red cell count or even for the polychromatic series because of the relatively high number of cells in these groups as compared with the few orthochromatic cells.

Most authors do not quote figures for this group individually, or their classification of cells is different from ours, so that a comparison of the orthochromatic group alone cannot be made. Correlation of our findings with those of others will be made for the total nucleated red cell group.

The polychromatic normoblasts constitute the largest group of the nucleated red cell series and are therefore statistically the most reliable. The average for Age Group I was found to be 12.59% (range 2.5-36.5%), for Age Group II 14.49% (range 5.0-24.0%) and for Age Group III 18.2% (range 4.8-34.0%). Although the individual counts show a considerable spread, this spread is not too wide to lose value for the individual case. The first month we considered separately and it shows the same variation of cells as has been noticed, to a less marked degree, in the previously described groups (table 3). The numbers for the first four days of life are considerably higher than the average during the following months and years. Following these first four days we find a marked drop to below the average which continues until the end of the second week, at which time the curve reverses its course and begins to rise, reaching average values for older children and adults around the third and fourth weeks. An explanation for this sharp decrease in immature red blood cells, expressing decreased activity of the bone marrow, may be found in the increased oxygen supply of the organism in the newborn baby, depriving the bone marrow of its physiologic stimulus for new cell formation which is known to be important in the fetus (Shapiro and Bassen[38]). The high figures immediately after birth are probably accentuated by the trauma of labor.[26, 37] We can correlate these findings with the peripheral blood where we find a similar decrease of red blood cells during the first two weeks of life with a leveling off in the following months (table 1).

The "physiologic anemia" of infancy around the third and fourth month of life (table 1) seems to be mirrored in the bone marrow where we see a lowering of the nucleated red cell count around this time (table 3). The data obtained from the study of the polychromatic normoblasts indicate to a certain degree the tendency of the total erythroid series because of the predominance in number of these cells as compared with the cells of other maturation levels.

Below is a discussion of the findings on the nucleated red cells as one group, thus avoiding the confusion and inaccuracies caused by different methods of classification. Chart 1 graphically describes the red series in our study, indicating the same tendencies as found in the polychromatic group. The individual counts are plotted in form of a scattergram and the mean is outlined. Frequency distribution, average and standard deviation are shown on chart 2. The average number of cells for Age Group III was found to be 23.12% (range 6.4-38.25%). For Age Group II the average value was 19.78% (range 8.75-32.0%). The data for the first month of life (Age Group I) show wide and characteristic variations with age. As shown on chart 1, there are high values for the first days of life with a drop around two weeks, after which the curve climbs and reaches average values by the end of the first month. At the 3 to 5 months of age period we find the lowering of the curve corresponding to the drop in the peripheral red blood cell count. Beginning with the end of the first year, age does not seem to influence the number of nucleated red cells as expressed by the small variations in the course of the line marking the average values for various age groups and by the standard deviation.

Myeloid Series

The cells of the myeloid series were studied individually (table 3) and as a group and the numerical variation demonstrated graphically (chart 3).

We have classified and statistically included the myeloblasts as the youngest form of the granulocyte group, although some consider them as the stem cell of the white cells while others regard them as the stem cell of all cells of the blood system (monophyletic and polyphyletic schools). We do not want to take position in this argumentation as the statistical significance of these cells with respect to the total myeloid series is very small

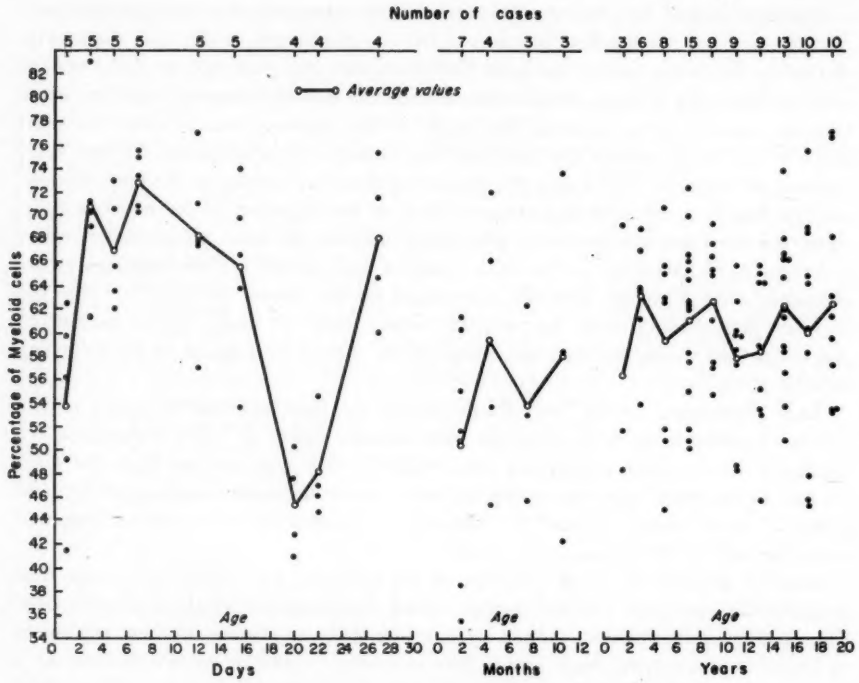

CHART 3. Scattergram and average values of myeloid series.

and they will not influence the percentile relationship of the total cell group due to their low absolute figures of occurrence. The numerical evaluations of the nucleated cells in toto or of any individual group, as done in this study, can therefore readily be compared with those of followers of either school.

The average value for the first year of life with the exclusion of the first month is 1.92% (range 0.25-3.25%), the average percentage for the following 19 years is 1.23% (range 0.0-3.25%). The trend during the first year is downward and this same trend continues during the following years (table 3). There seems to be no consistent tendency during the first month. One must consider the small number of myeloblasts encountered in a count of four hundred cells, which makes the findings statistically of little significance. The trend of diminishing immature cells with increasing age of the individual seems, however, logical and a very similar observation has been made in the erythroid series.

The leukoblasts do not seem to show any consistent variation in children of different

age groups. The average percentage for Age Group I is 1.86% (range 0.25-4.25%), for Age Group II 1.11% (range 0.33-2.5%) and for Age Group III 1.44% (range 0.0-4.0%).

The promyelocytes, because of their greater number, lend themselves to statistical treatment. Average values for this cell group are shown on table 3. The figures clearly indicate the higher activity of the bone marrow in the formation of these cells during this early period of life. The values for the remaining months of the first year and for the following 19 years show the decreased activity in the formation of these cells and also the much narrower range of variation during later years. It might be pointed out that in the counts on the infant group (first month of life) the average value was found to be 3.77%, with a range from 0.0 to 13.75%, a much higher value than for the older age groups (0.68% for group II and 1.8% for group III). Some authors[35] report higher figures for this cell group, but do not list leukoblasts separately, thus most likely including at least part of these cells in this group and also, probably, the younger cells of the following group, the myelocytes.

The identification and classification of the myelocytes offer certain difficulties, as mentioned previously. The average value for Group I is 18.14% (range 7.0-24.75%) and for Group II 16.73% (range 12.0-26.5%). With the exception of the first year, there seems to be no age determined tendency to decrease with progressing age (Kato,[9] Jacobsen[20]). The average percentage is 16.46% (range 8.5-25.25%).

To summarize the findings on these cells, much error is possible because of uncertain limits of classification. The cell definition seems to be the reason for discrepancy between various authors. Cells showing a kidney-shaped indentation of their nucleus which appears of equal thickness throughout or narrow at the point of indentation are classified in this study among the metamyelocytes whereas others placed many of these cells among the myelocytes.

The average value of the metamyelocytes from one to 19 years inclusive is 23.27% (range 14.0-34.25%). The observation of the curve of the average during the first month of life shows considerable variation (range 10.75-40.0%) with an average of 25.64%.

Let us now analyse some of these variations and consider their importance with regard to the bone marrow activity in certain cell groups. During the first days of life we see a sharp incline of the curve, which may lead us to the conclusion that the myeloid bone marrow activity is low at birth and increases rapidly thereafter. If we consider, however, the very high nucleated red cell count with its rapid drop during this same period and take into consideration that we are doing differential counts and express the cells in percentages, we see that an increase in the number of red cells will automatically decrease the percentage of the white cells counted per hundred and vice versa. Nevertheless, for the purpose of establishing "normals" we may state the averages for the metamyelocytes are low on the first and second day of life (20.3%), increase to a high during the seventh and eighth day (35.12%), then drop rapidly to a low (14.25%) on the 20th and 21st day and then approach the average of 23.27%. An explanation for the drop on the 20th and 21st day may again be found on a statistical basis rather than an actual drop in the absolute figures of the myeloid series, inasmuch as the lymphocytes show their peak values during this period thus reducing other cell groups in the percentage value. There seems to be a peak of the values for metamyelocytes during

the three to five months period, but here too we have to consider the physiologic anemia of the newborn infant (chart 1 and table 3), which shows a dip in the red cell series and thus would automatically increase the white series or its foremost exponent, the metamyelocytes.

The polymorphonuclear neutrophils average 12.9% of all nucleated cells, if we consider the first to the twentieth year. The range is from 4.5 to 29.0%. The total average for Age Group I is 9.33% (range 2.25-19.0%) and for Age Group II 7.25% (range 2.5-15.5%). In examining these figures we find that they show an ascending tendency similar to the metamyelocyte group (table 3). It seems logical to find these mature cells increasing in number in the older age groups. The variations during the first month of life are not as marked and consistent as in the metamyelocytes, which might be expected

TABLE 5

EOSINOPHIL GRANULOCYTES

	1st mo.		1–12 mo.		1–19 yr.	
	Aver.	Range	Aver.	Range	Aver.	Range
Promyelocytes	(Very few seen, on many counts of 400 none found)					
Myelocytes	0.74	0.0–3.0	0.41	0.0 –1.5	0.48	0.0 –2.25
Metamyelocytes	1.74	0.0–4.25	1.70	0.0 –3.25	2.21	0.25–6.25
Polymorphonuclear Cells	1.2	0.0–2.75	0.59	0.0 –1.75	0.84	0.0 –3.5
Total (incl. Promyelocytes)	3.77	0.0–7.0	2.58	0.25–4.75	3.58	1.0 –9.75

for two reasons, one being the smaller number of polymorphonuclear cells counted per individual slide which decreases the statistical accuracy, and secondly the fact that any dilution with peripheral blood would influence the polymorphonuclear count considerably whereas the counts of the other cells would be affected to a minor degree. The change in percentage of the other nucleated cells (nonpolymorphonuclear) and of the polymorphonuclear cells due to the dilution factor will be in the opposite direction and at the same ratio as the absolute figures of the polymorphonuclear cells to the other nucleated bone marrow cells (13:87), or the change will be 7 to 8 times as large in this individual group as in all other groups together. It seems that during the first four days we see an increase in these cells, as we have described in the metamyelocytes, which gradually levels out to the average which for the first year is lower than for the following years (table 3).

The numerical relationship of the eosinophil granulocytes at different maturation levels is similar to that of the neutrophil group. Again we notice the greatest variations during the first month. The eosinophil promyelocytes occur in such small number that in many counts of four hundred nucleated cells none were found, in the rest of the slides we found between one and two cells (0.25-0.5%). The myelocyte group is larger; there were only a few counts where no eosinophil myelocytes were encountered. The average for the first year with the exclusion of the first month was 0.41%, with a range from 0.0 to 1.5%, for the group from one to 20 years the average was 0.48% with a range from 0.0 to 2.25%, and for group I the average was 0.74% (range 0.0-3.0%). The eosinophil metamyelocytes show great variations during the first month, like all other cells, rang-

ing in number from 0.0. to 4.25% (average 1.74%). The average for Age Group II was 1.7% with a range from 0.0 (in only one case) to 3.25%. The average for Age Group III was 2.21% with a range from 0.25 to 6.25%. The majority of cases were between 1 and 3%; only very few cases were below 1%, one case each at 6.25 and 5.0%, and two cases at 4.75%. The eosinophil polymorphonuclear cells show an average of 1.2% for the first month and 0.59% for the first year and 0.84% for the following 19 years. Only very few counts showed no polymorphonuclear eosinophil cells and the range of this group was not very widespread.

The data for the eosinophil cells are summarized on table 5. Essentially the findings in the literature are similar to ours, yet the small number of occurrences of these cells, with

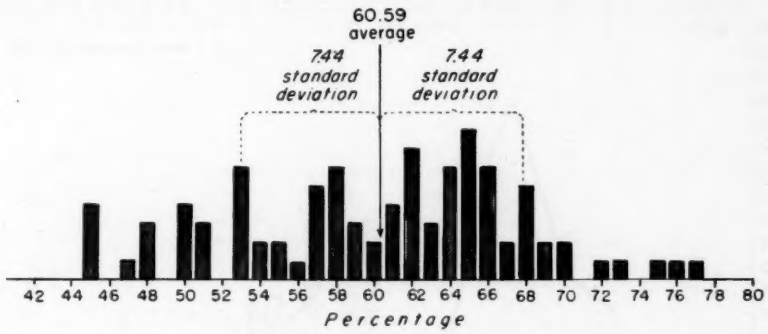

CHART 4. Frequency distribution and standard deviation of myeloid series.

a relatively great variation within that small number, makes it impossible to attribute great statistical value to these findings.

Between 0.0 and 0.75% basophil granulocytes were found on our counts of four hundred cells. It is impossible to establish the relationship to age and to statistically evaluate this cell group in this study because in many counts of four hundred cells no basophil cells were seen. It seems that in the group of older children and young adults we found fewer slides without any basophil cells. It is only conjectural to state that this indicates a more frequent occurrence of these cells in the older age groups. To establish such a fact a larger number of cells would have to be counted per slide.

The numerical relationship and variations of the total myeloid group are conditioned by the numerical behavior of all myeloid cells. They are, however, essentially dictated by the pattern of its largest representative, the metamyelocytes.

The average for the total group is 60.59% with a range from 45.0 to 77.0% in the period from one to 20 years (tables 3 and 4, charts 3 and 4). The findings for Age Group II are 54.38% (range 35.5 to 73.5%). The greatest fluctuations occur during the first month of life, with a rapid increase in cell numbers during the first four days of life, and a drop in the second half of the first month (chart 3). During the following months of the first year we note a gradual increase until about the third year when figures close to the established average value are reached. Throughout the later years there seem to be no marked changes. The sharp increase during the first few days of life might in part be only a statistical phenomenon caused by the sudden drop in the cells of the red series. We also know that during the following days there is a progressive

increase of lymphoid cells in the blood as well as in the bone marrow, which might again decrease the number of myeloid cells found per hundred nucleated cells as seen on the 20th and 21st day of life (chart 3). To which degree these changes are variations in the absolute figures of one or both of the cell groups or to which degree one of the cell groups shows an increase or decrease in percentage only relative and corresponding to the other group remains to be established. The percentile relationship of these cells seems to be constant and established by this study and verified by the findings of other authors. During the months of the second year of life we also know from the blood picture that the myeloid cells begin to exceed the lymphocytes and it is therefore not surprising to

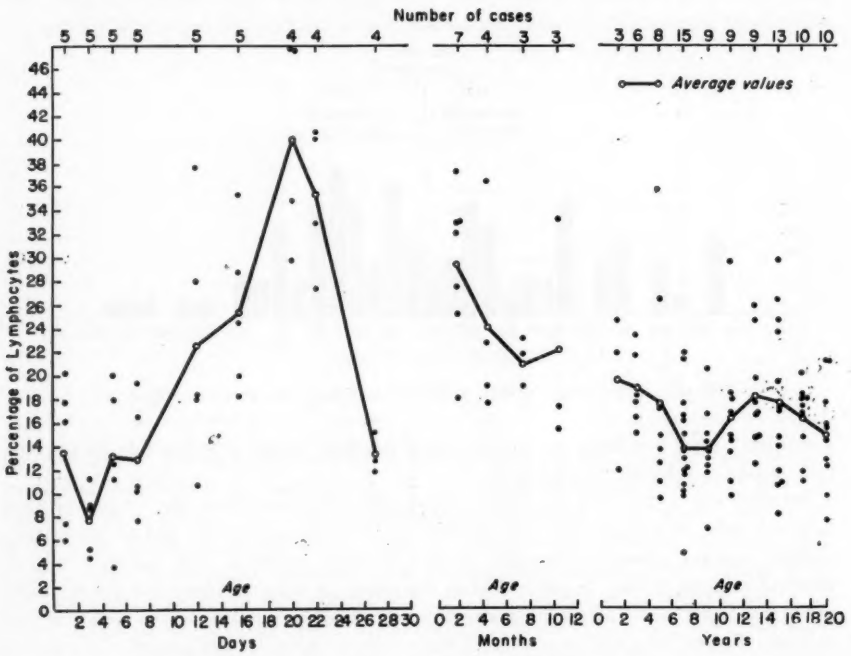

CHART 5. Scattergram and average values of lymphocytes.

see them increase in number in the bone marrow. From the second year on, the blood picture with relation to the lymphocyte-myelocyte ratio does not vary, neither does the numerical relationship of these cells in the bone marrow (table 3 and chart 3).

MYELOID-ERYTHROID RATIO

The myeloid-erythroid ratio is the mathematical expression of the numerical relationship of the granulocyte and erythrocyte groups. Since, as mentioned before, different investigators do not agree on the numerical expression of individual cell groups because of discrepancies in the interpretation of cell definition and nomenclature, the consideration of the total groups and particularly of the relationship of the two groups to each other is of much greater significance. The myeloid-erythroid ratio was obtained by dividing the

figures for the percentage of all cells in the myeloid series by the percentage of erythroid cells, thus always obtaining 1 as denominator. The ratio is therefore expressed by a single number.

The average myeloid-erythroid ratio for the counts on individuals from one to 20 years was found to be 2.94 (tables 3 and 4), with a range from 1.22 to 11.78 (next highest figure: 5.22). Again, as observed in the individual cell groups, the greatest variation occurs during the first month of life, namely, a sudden increase of the ratio from below the average (1.85) to far above the average (11.18) during the middle of the first month. This sudden increase of the myeloid-erythroid ratio corresponds to an increase of the myeloid elements (chart 3) and a simultaneous drop in the erythroid elements (table 3 and chart 1). During the latter part of the first month the ratio approaches the average level, due to the lowering of the percentage of the myeloid elements. The values for the

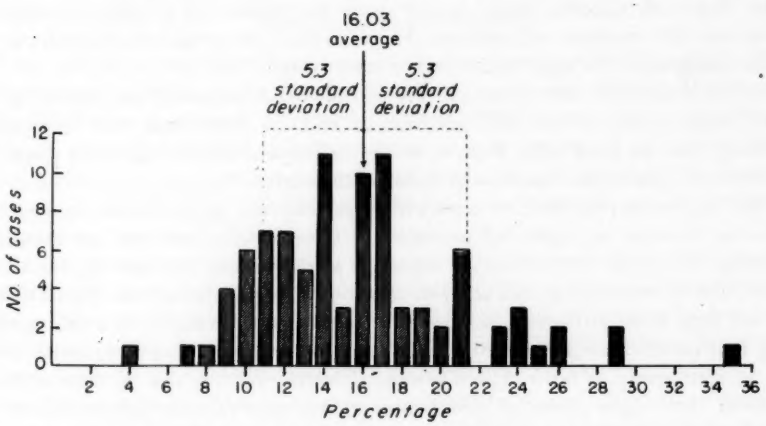

CHART 6. Frequency distribution and standard deviation of lymphocytes.

erythroid series remain essentially level at this age period. From then on, throughout the rest of the first year and the following years up to the twentieth, the curve for the myeloid-erythroid ratio maintains an average level.

LYMPHOCYTES

The average percentage of lymphocytes found was 16.03, with a range from 4.75 to 35.75% (charts 5 and 6, tables 3 and 4). There seems to be a decrease in the number of lymphocytes with increasing age, a phenomenon which might again at least in part be explained by the method of aspiration used. The standard amount of 1 cc. of marrow fluid will produce less dilution with peripheral blood as the marrow cavity grows with increasing age of the child. Therefore the elements which are present in the blood in larger number than in the bone marrow will influence the marrow specimen to a lesser degree as the amount of dilution decreases.

As in other cells, the greatest variation again occurs during the first month of life (table 3, chart 5). We notice first a low lymphocyte count, which increases rapidly to reach a peak of 40.0% on the twentieth day. This corresponds to the granulocytic pre-

dominance in the peripheral blood during the first days of life, followed by lymphocytic predominance in the second part of the first month. We then see a drop during the first and second year which corresponds to the lowering of the lymphocytes in the peripheral blood. From then on the number of lymphocytes remains on an even level (Kato,[9] Jacobsen,[20] Veeneklaas[27,28]).

Cells Occurring in Low Numbers

The following cells occur in very small numbers in the bone marrow and their statistical evaluation, therefore, is difficult and of little significance since any pathologic increase would easily be recognizable upon inspection of a smear.

The monocytes occur in such small number that in many counts of four hundred cells not a single monocyte was encountered. In order to evaluate these cells numerically one would have to count not four hundred but several thousands of nucleated cells on every slide. Only such elaborate studies would assure the presence of a sufficient number of these rare cells to notice and interpret changes in their percentage of occurrence in the various age groups. The range in our series is from 0.0 to 0.75%.

Similar observations were made on reticulo-endothelial and on plasma cells (Fig. 6). Their range is from 0.0 to 1.25% and from 0.0 to 1.0%, respectively, with many counts showing none of these cells. Reports on the reticulo-endothelial cells show great discrepancies in nomenclature and interpretation of these cells.

The megakaryocytes must be considered separately and in a different manner. We have not reported any figures of occurrence of these cells, because with our method of counting on a slide, they would not represent a true picture. It would be much more correct not to record these cells at all in numerical investigations of this type since they are not only small in number and therefore not accurately evaluated in a cell count of only four hundred, but their uneven distribution on the smear (periphery) makes counting in relationship to other cells inaccurate. It seems that the size of these cells and probably their sticky character places them in our type of slide preparation on the periphery of the smear, particularly toward the feather end, and if we examine the cells under high power with oil immersion, as other cells are counted in the differential count, it depends entirely on the location of the microscopic field with relation to the slide margin of whether or not one will encounter these cells in larger numbers. From a practical point of view it is therefore more valuable to briefly search for these cells under low power magnification and consider them as "absent, markedly or moderately decreased, normal or increased" rather than to try to enumerate them. One might with some experience reach fairly comparable estimates, but these depend, of course, on the subjective interpretation of the examiner.

Many attempts have been made to find accurate methods of counting megakaryocytes. An excellent summary of the various procedures was written by Pizzolato.[39] He described the various methods used and devised his own. The results of different counting procedures are so variable that they seem to lose significance. Dameshek and Miller[40] found an average of 182.5 per million nucleated cells using the smear method, Japa[41] 2-5000 per million, using an imprint method, Limarzi[42] 58.8 per million, using the smear method, and Pizzolato,[39] using his own chamber (hemocytometer) method, averaged 211 megakaryocytes per million nucleated cells. Another summary appeared in 1948 by Berman et al.[43] It is a brief review of the customary methods of megakaryocyte determination,

with a conclusion that none is satisfactory. The use of bone marrow sections obtained by sternal aspiration is recommended as a satisfactory method. Extensive work in this field has been done in animals by Mayer and Ruzicka[44] who studied the number and position of the megakaryocytes in microscopic bone marrow sections.

Mitotic forms of the red and white series were observed (Figs. 3 and 7) but not statistically evaluated. Here too it might be interesting to do a study on larger numbers of cells than were counted in this series in order to obtain a large enough number of mitotic forms in various stages for statistical treatment. An evaluation of mitotic curves, examination of the frequency of occurrence of mitosis and of the various phases of mitosis in different cells and particularly in cells of different maturation levels, would be of interest and reports by Segerdahl,[11,12] Leitner,[33] Fieschi[45] and Japa[46] and others are available on this subject. It seems, however, that variations with age in the frequency of occurrence of mitosis were not studied.

Review of the Literature

The difficulties which one encounters in an attempt to compare findings of different investigators can be appreciated if the great variations in nomenclature, definition and classification are considered. In order to properly value the report of an investigator, it is necessary to know his method of bone marrow collection including location, amount, and preparation, his statistical method, and finally his case material—the number of punctures, the age of the individual and the means by which the health of these individuals was determined. These questions are taken up below.

In this review we are bringing the facts concerning the methods employed by authors whose publications were available to us and are comparing their findings with ours as far as they are of importance because of their disagreement with us or confirmation of our results. A very detailed evaluation of the findings of other investigators and statistical comparison was reported in a thesis.[10] The purpose in discussing various reports is to establish "normals," explain discrepancies between the findings of various investigators so far as that is possible and thus find means of reducing the sources of error in future work. Because of the great discrepancies in classification and the lack of an accurate description of the cells in many publications, it is often necessary to compare "cell groups" rather than individual cells.

Tecilazic[26] (1935) studied 30 newborn infants and made several punctures on each during the first seven days of life. The condition of mother or infant was not stated, but blood smears were done on each child at the same time as the marrow study. The marrow was obtained from the tibia on alternating sides each day. The amount withdrawn was just sufficient to make a smear. The author used May-Grünwald-Giemsa stain and counted one thousand cells. The author mentioned in the text that many destroyed or unidentifiable white cells were found, particularly in infants of one or two days of age. The red cells were not so affected. The alteration of cells may have been caused by the method of preparation of the specimen. This probably influenced the results materially, since his values for the erythroid cells are very high, for the myeloids much lower than expected and the myeloid-erythroid ratio in this author's report was below one during the first days of life, a finding which is not confirmed by this study or by other investigators. The characteristic tendency of the erythroid cells to markedly decrease and the myeloids to increase in number during the first days of life is well borne out

by this author. The actual purpose of the publication was a comparison between bone marrow findings in full term and premature babies.

Debré, Lamy and Sée[47] (1935) studied 10 cases—six males and four females—all healthy children (one newborn infant, two infants 3 months of age and the others 2, 3, 6, 7, 12, 14 and 15 years of age, respectively). The blood was not studied. A "very small quantity of marrow" was aspirated. The staining technic was not indicated and no statistical evaluation was made. The authors did not discuss their method of cell classification but, e.g., do not use the term leukoblast, probably including this cell among the myeloblasts. The authors stated that they did not find remarkable changes in the bone marrow of children above 6 months of age. The only newborn child they examined showed a high nucleated red cell count. The low number of cases in their study does not permit evaluation of the trend of change with age during the first and second year, but the figures, if considered grossly, correspond to those found in this report.

Kato[9] (1937) studied 51 infants and children between the ages of 1 month and 13 years of age. None was below 1 month. Physical examination and blood study were done to rule out illness. Kato aspirated 0.1-0.2 cc. of marrow fluid, counted five hundred cells and mentioned several methods of staining. The statistical evaluation consisted of the compilation of average figures by age groups (1-2 months, 3-12 months, 1-2, 3-4, 5-6, 7-10 and 11-15 years). Cell classifications were discussed in the article. This author's failure to study the first month made him miss the important findings of this age group. Furthermore, his subdivision of cases during the first year into only two groups (second and third months and fourth to twelfth month) conceal the dip of the erythroid curve during the third to fifth months.

Kato observed a decrease of the erythroid count with age, an observation which we have not made and which is not corroborated by Jacobsen,[20] Vogel and Bassen[29] or Veeneklaas.[27, 28]

Kato's figures for the older cells (segmented forms, staff cells and metamyelocytes) are lower than ours, whereas his figures for the younger cells are higher. We may attribute these differences to the different technics: Kato aspirated only 0.1 to 0.2 cc. of marrow, thus had much less peripheral blood dilution and introduction of mature or almost mature cells from the blood into the bone marrow than with the method used in this study. There is no definite trend at different age levels in his figures of promyelocytes but one has to keep in mind that he did not examine children below one month of age. His comment that in older subjects the marrow shows more staff forms and fewer metamyelocytes is substantiated by his table. In general the younger cells of the series are more numerous in the younger age group, an observation made by him and by others as well as by us. It is interesting that this tendency to change in number at different age levels is noted with consistency on the younger cells during the first months of life only, whereas in the older and more mature cells it can be observed throughout the entire observation period. The fact that this variation is not apparent in the younger cell groups may be explained statistically by the low number of these cells rather than an actual deviation from the expected numerical pattern.

The neutrophilic segmented forms vary between 4 and 7%, with the higher figures in the older children. The increase is parallel to that of the staff forms and Kato considers this increase in the older individuals sufficiently marked to be significant. His generally lower figures for these cells may be due to the smaller amount of marrow aspirated by this author (0.1-0.2 cc.).

The total myeloid cell count shows figures similar to ours. It seems that the difference in method of aspiration does not influence the total white or red cell count as much as it interferes with the number in the subgroups. That is understandable as the dilution factor would enter in the small subgroup or polymorphonuclear cells, diluted only with this type of cell from the blood, much more than it would influence the total myeloid count which, although increased by the segmented cells, is decreased in total by the influx of lymphocytes into the bone marrow.

Veeneklaas[27, 28] (1938) reported on bone marrow punctures performed on 101 children. In his articles in the *Maandschrift,*[27] the patients were grouped in 3 categories: Group 1, 3 children below 14 days, Group 2, 65 children between 14 days and 3 years and Group 3, 33 children above 3 years. It is obvious that the three cases in the first group were not sufficient to make average values statistically significant, especially after finding such great variations during this age period. In this publication Veeneklaas also failed to indicate the exact ages by days of these three children, as well as the range for the group above three years. In his thesis,[28] however, the individual cases were tabled and we find that the first group consisted of children 6, 7 and 14 days old and that the oldest child in the third group was 14 years. The great importance of this detail will be noted in the numerical evaluation of this author's findings. The author withdrew just enough marrow fluid to see the first drop appear in the syringe, and used May-Grünwald-Giemsa stain. A very detailed statistical evaluation of his findings is included in the article. The author stated his definition of each cell.

Veeneklaas reported for the erythroid series average findings of 12.0, 13.3 and 14.0%, respectively, for his three groups. In examining the findings of his five cases below one month of age we find that they correspond with ours; Veeneklaas, however, could not show the significance of his findings since he had only five cases. If we consider his data for Group 2 (14 days to 3 years) individually we find that, although minimal, his figures too show a decrease in the nucleated count in the three to five month group. His findings in older children, although lacking any marked tendency of increase or decrease in number, are lower than ours.

The averages for the myeloid series are 67.0% for his first group (below 14 days of age), a finding which is similar to ours (chart 3, table 3). In his second group (from 14 days to 3 years) he found 47.5% and in the third group (from 3 years on), 56.9%. The increase from the second to the third group is similar to the findings in this study. It is regrettable that this author did not tabulate his cases individually in his publication in the *Maandschrift* and that he did not have more infants below one month of age in his study. His findings on individual cases, as tabulated in detail in his thesis,[28] are a perfect match for this study. The interesting and consistent findings of the first month and during the 3 to 4 month period were concealed in Veeneklaas' publication because of his small number of cases in the first month and his grouping of the older cases.

In evaluating the findings for the individual cells we encounter the usual difficulty of discrepancy in classification; this author separates metamyelocytes from staff forms, but if we consider these two cell forms together, his findings correspond closely with our metamyelocytes.

Veeneklaas found the following ratios: Group I: 67:12-5.6, which is similar to ours and to Shapiro and Bassen's;[38] Group II: 47:13-3.6 and Group III: 56:14-4.0, again about the same as ours.

Vogel and Bassen[29] (1939) presented 41 cases, 19 boys and 22 girls, varying in age

from one day to 12 years, The authors tabulated their findings but did not evaluate them statistically because, as they stated, of the small number of cases and the great variation of figures. Normal newborn infants and children admitted for tonsillectomy and normal on physical examination were studied. No mention of parallel blood studies was made. The authors collected 0.1-0.2 cc. of marrow fluid and stained the slides with Jenner-Giemsa stain. They counted five hundred cells. A description of the authors' cell definition and nomenclature was included in the article.

On the 12 punctures made on children below the age of 1 month they found a range of 4.6 to 38.2% of the erythroid series with no noticeable tendency in the distribution of the counts. Above the age of 1 month they had 29 punctures; they felt that this series was too small for statistical analysis but, in averaging their figures for the erythroids (23.1%), we find that they correspond exactly to our average of 23.12%. The same is true if we survey grossly the numbers of the myeloid series. We find the tendency of low figures during the first days of life, with an increasing number up to 2 weeks, a marked drop in number of these cells in their 3 cases between 12 and 24 days and then a fairly even course. The figures for the lymphoid cells correspond also with ours showing lower figures during the first days of life, the highest during the second part of the first month with a progressive decrease with advancing age of the child.

Diwany[48] (1940) reported on only five cases in the second and third years of life and 10 cases in the fourth to sixth year. Thirteen of them were male and two female. They were healthy children as determined by primary blood study and physical examination. The article does not bring statistical evaluation of the findings or cell definitions and nomenclature. Giemsa or May-Grünwald-Giemsa stains were used and 0.1-0.2 cc. of marrow fluid were aspirated. This author's findings show great similarity to ours, the small deviations being probably due to his very small number of cases.

Shapiro and Bassen[38] (1941) studied 35 normal full term infants, 14 males and 21 females. Two punctures were performed on each child, one during the first 24 hours of life and the other one week later. This gives us data from 70 punctures distributed over two well selected days. Statistical findings of this sort are most significant. The authors found no important variation in the counts taken on different hours during the first day of life. Sex, weight, feeding method or the presence of physiologic jaundice seemed to have no influence on the cell counts. Shapiro and Bassen's findings correspond with remarkable accuracy to ours. Blood counts were done on all babies. The authors used a short needle and aspirated enough to have marrow appear in the neck of the syringe. Jenner-Giemsa stain was used and five hundred cells were counted. All cases were tabulated and the average values calculated. The results were also described graphically. The nomenclature and classification were the same as in a previous article by Vogel and Bassen,[29] and offer some difficulties: e.g., Shapiro and Bassen found 0.1% megaloblasts on the first and eighth day of life. Veeneklaas and Vogel and Bassen, as well as the authors under discussion, classify their erythroid series into megaloblasts, erythroblasts and normoblasts. These differences in classification make accurate comparison of subgroups difficult; however, the total nucleated count reported in these two studies corresponds to our findings, proving that the discrepancy of the findings in the subgroups is a question of nomenclature and classification rather than actual differences in the cell counts.

Shapiro and Bassen's findings show an increase during the first week of life of 60.6% to 77.4% of the myeloid series and from 3.8 to 6.2% of the lymphoid series. They aspirated only very little bone marrow and, like Tecilazic, probably obtained very little

dilution. They note an increase of lymphocytes during the first few days of life and believe that the total number of lymphocytes in the blood does not change materially but that the myeloid cells decrease sharply in the blood, causing an increase in percentage but not in absolute number, of the lymphocytes. The decrease of myeloid elements in the blood is then to be explained with a decreased release of myeloid cells into the blood stream.

Jacobsen[20] (1941) divided his cases into four age groups: 2 to 5 years (6 cases), 6 to 9 years (7 cases), 10 to 14 years (5 cases) and 15 to 19 years (7 cases). He aspirated 0.5 cc. of marrow fluid and counted two thousand cells on each slide stained with May-Grünwald-Giemsa solution. The cells were well analyzed statistically and the cell definitions thoroughly discussed. The health of the individuals was carefully checked; blood studies were done simultaneously with the punctures. His findings are in close correlation with ours.

Osgood and Seaman[1] (1944) reviewed the available literature most thoroughly and ended their paper with a request for more studies to substantiate the present conception of normal standards for the cellular composition of the bone marrow under clarified conditions of nomenclature and classification. A table of "tentative recommended standards" summarized the findings collected from the literature. The data were divided into two groups, (1) as obtained by withdrawal of large amounts and (2) as obtained by withdrawal of small amounts of bone marrow. They did not describe the cells but stated that the nomenclature of Osgood and Ashworth's[49] Atlas was used.

Osgood and Seaman came to the following conclusions: "It is apparent that the differences in differential cell counts in children and adults are relatively slight compared to the variations in the figures of different investigators of bone marrow on the same age group. If there is any difference it is a slightly higher percentage of the polymorphonuclear neutrophil leukocytes in children." They further stated that it was hoped to establish standards when this study was undertaken but that this goal must await further investigation.

We quite agree with this statement since at the time Osgood and Seaman wrote their paper (1944) no extensive study on bone marrow in infants and children existed to their and our knowledge. We believe that a definite tendency of the numerical relationship and its alterations during the period of growth has been established in the present study, in spite of the wide variations in individual counts done by one investigator and the often even greater discrepancies between the findings of different authors. In comparing the findings of other investigators and combining their findings, covering only some phases of the problem, we find not only a verification of our study but also see that each one of the investigators hit upon some characteristic finding which, put together, produces the total picture of the cellular composition of the bone marrow in infants and children.

Segerdahl[11, 12] (1935) studied 52 men, 40 women and 18 old people. All were healthy adults as tested by physical examination and blood picture. The exact amount withdrawn was not mentioned, but it had to be enough to make a smear first and then be put into a tube with oxalate. The method of staining was not discussed. A very detailed and exact statistical evaluation was included in the review, as well as a detailed description of cells and an extensive review of the literature.

This author's data for the erythroid cells are lower than ours, her myeloids occurred in somewhat higher numbers and the figures for the lymphoid cells are about like ours.

The considerable age difference of the subjects, the third group consisting of "old persons," must be taken into consideration, and also that she withdrew "a certain amount" of marrow fluid, using the first drop in the needle for the smear from which the count was made, thus using the most diluted part of her puncture material, and this was probably the reason for her high myeloid counts.

Vogel, Erf and Rosenthal[14] (1937) studied 21 adults. Exact ages were not given. The series included 13 females and 8 males. They were all hospital employees and considered healthy; no blood studies were made. The amount aspirated was either 0.1-0.2 cc. or 2.0 cc. and about half the cases were used for each method, but possible differences in results with these methods were not evaluated. The authors called the second method essentially the same as that used by Young and Osgood[50] and Reich.[51] Five hundred cells were counted on each slide. The marrow obtained by the second technic was centrifuged for 5 to 10 minutes. Jenner-Giemsa stain was used. The average values for the percentages of occurrence of the cells were calculated, but in contrast to most other authors the percentile relationship of the white cells was considered separately and the nucleated red cells per hundred white cells were calculated. The figures for all cells were therefore about 25% higher than if the red series had been included with all nucleated cells. Description and classification of each cell type were given. They found an average of the total nucleated red count of 29.7%, with a range of from 8.2 to 83.0%. Considering their statistical methods and deducting 25% we arrive at figures very similar to ours. Their total myeloid cell group (89.57%) is somewhat higher than our data indicate, and their lymphoid cell correspondingly lower. The polymorphonuclear cells occur in particularly high numbers, a factor which might be produced by the high degree of dilution of the bone marrow with blood which would be expected from the use of the second method. We also have to consider different ways of making smears by the first method. One can use the total material withdrawn (0.1 to 0.2 cc.) or use the first drop obtained from the needle, as Segerdahl[11,12] did, which should show more dilution than a mixture of the total material. A separate analysis of their findings as obtained by the two methods of bone marrow collection would seem indicated.

Arinkin[15] (1929) studied the marrow only of adult patients who had a normal composition of the peripheral blood and no disturbances of inner organs. The amount aspirated was indicated by the statement that the first few drops withdrawn were used for smears. The slides were stained by Leishman or Giemsa method. The reported findings by this author approximate our findings reported in table 4.

Lichtenstein and Nordenson[52] (1939) studied 8 newborn infants but did not give the exact age and health of these patients or the method of marrow aspiration. The authors stated that the bone marrow composition in the eight full term infants studied did not vary materially from that of adults. The erythroid elements counted up to 19%, a figure very similar to that found in this study. In Nordenson's[53] study on adults about the same figures were reported.

Holmes and Broun[54] (1932-33) studied the bone marrow of three adults and Tempka and Braun[55] (1932) that of seven adults. This small number of cases did not seem to have sufficient statistical significance for purposes of comparison.

Kramar and Hensch[56] (1925) studied the bone marrow of 41 newborn infants and infants (2 weeks to 21 months) of whom only three were healthy; their exact ages were not given.

Young and Osgood[50] (1935) studied 28 normal male adults and brought average

values. Their method consisted of aspiration of 1 or 2 cc. of marrow fluid. No children were studied.

Some of the preceding reports, although covering studies on adults, are briefly discussed in this paper because of their value for comparison with our findings in the 1 to 20 year age group. These reports give additional proof to the assumption that the findings in the 1 to 20 year age group do not differ materially from those obtained on adult bone marrow.

In summary it may be said that the data obtained from the cells of the myeloid and erythroid series in toto correspond fairly well to those found by other investigators. In comparing specific subgroups rather than the total group the discrepancies between the individual investigators are much wider. This once again points to the need for clarification of the question of cell definition and classification and standardization of technic. Once these standards are established the study of the bone marrow pattern will become of even more help in arriving at a diagnosis. The wide range of individual cell counts calls for caution when considering pathologic cases. We must consider the total pattern rather than the reports on one individual cell group in order to be able to establish a diagnosis.

Discussion

The knowledge of the cellular composition of the normal bone marrow is a prerequisite for the interpretation and understanding of the bone marrow in disease. Although a number of reports in the literature have described findings in the bone marrow of children, the articles available covered only certain phases of the problem, considered limited age periods or had shortcomings in some other way, thus making them of only limited value for the establishment of "normals."

The interesting observations of Shapiro and Bassen[38] and of Tecilazic,[26] for instance, are limited to the first week of life. Veeneklaas[27, 28] and Kato[9] give information mainly about older age periods (above one month); Vogel and Bassen's[29] cases are distributed over a long period (birth to 15 years), but there are no cases between the ages of 1 month and 2 years. Yet the reports on 12 individual cases reported by these authors and the 5 reported by Veeneklaas[27, 28] during the important first month of life contribute information if incorporated into a larger series, but are too small in number, if used alone, to indicate any trend. Thus by pooling all the information available the number of observations is increased and the correctness of the findings is verified by comparison with independent reports.

In order to establish "normals" for future comparison some criteria should be met. The subjects must be healthy individuals, the method and technic of puncture, preparation of the marrow smear as well as staining method and number of cells counted must be described in sufficient detail so that they can be accurately duplicated by others. The standardization of the amount of aspirated material is of greatest importance. The number of bone marrow punctures must be large enough to have statistical significance and the distribution of the punctures over the various age groups must be statistically adequate. In the evaluation grouping of the cases according to age must be of such spacing as to permit discovery of essential and characteristic age-conditioned cell variations. The cell classification, definition and nomenclature must be described and preferably illustrated to eliminate all doubts about the author's cell identification until such time as a universally accepted system is established. Such unification is now in preparation.[2,3]

In this study it was attempted to consider all the preceding factors and also to include all available literature reports in order to increase the value of the findings of this study and to show by such comparison the correlation of our findings to those of others.

In reviewing the findings of this study, extending over a period from birth to 20 years, we note that the changes occurring after the age of one year are of minor extent and little statistical significance (charts 1, 3 and 5). We believe we are justified, therefore, in taking the data obtained during the period from 2 to 20 years for the calculation of the average values for the occurrence of the various cells during this age period. These figures are summarized in table 4.

The data reported in this table are discussed in detail in the text of this paper and correspond essentially to those found in the literature.

The cell counts on infants below one year and particularly below one month showed wide and constant variations with age and warrant special consideration.

The number of nucleated red cells during the first and second days of life was above that established as normal averages (23.12%). From then up to the fifteenth day there was a marked decrease, followed in turn by an increase to average values. Lower figures were again recorded during the third to fifth months. Among the individual cells of this series the polychromatic normoblasts showed variations identical to those of the total red cell group. Pronormoblasts and basophilic and orthochromatic normoblasts showed similar findings but the fluctuations in number became less marked and statistically less significant with the smaller number of cells. Over the entire span of 19 years there seemed to be a tendency for the younger cells to decrease in number with progressing age and for the older cells to increase during the same period. This variation in percentage was minimal, yet it occurred with remarkable consistency.

The observations on the myeloid series brought, similarly, strong and constant changes during the first month of life, with less significant variations during later months and years. The values for the first and second days of life closely approached the average figures (60.59%); the following days we saw a marked increase in number of myeloid cells with a drop around the twentieth day, followed by a rise to average figures by the end of the first month. From then on there was little deviation from the average up to the end of the observation period (20 years). As to the individual cells in this group, the metamyelocytes, which form the largest part of the series, showed the same pattern as the total group. The smaller groups of the myeloid series showed findings similar to those of the total group, but again the variations were not as marked because these cells occurred in much smaller numbers. In considering the total period of observation there seemed to be again a tendency of a decrease in the number of younger forms and an increase in the number of older forms.

The myeloid-erythroid ratio showed during the first and second days lower figures followed by a sharp rise up to the end of the second week (11.18) when the values again fell. Thereafter, the deviations of individual counts from the average bore no relation to the age of the child.

The lymphocytes varied in number from a low on the first to eighth day to a high of 40.0% around the twentieth day. During the first and second year there was a gradual decrease (corresponding to the decrease in the peripheral blood), reaching the average level (16.03%) at around 2 to 3 years of age.

Basophilic granulocytes, plasma cells, megakaryocytes, monocytes and histiocytes oc-

curred in small numbers and no tendency of the numerical variations of these cells with regard to age could be noted in these counts.

In the practical application of the presented facts we have to consider the wide variations of the individual cell counts on cases in the same age group, the variations on counts done on one individual and even on counts performed on the same slide (uneven distribution of cells). These variations do occur even when identical methods are used by one individual and they are unavoidable. Segerdahl,[11, 12] reporting on the results of the examination of a large number of bone marrows of adults, states that "the differential counts of bone marrow slides carry a great uncertainty. The greatest source of error is that in several punctures on the same individual the results may be different. These sources of error are unavoidable and therefore it is not worth while to spend greater efforts on the refinement of the methods of counting." Osgood and Seaman,[1] as well as Poncher,[7] also emphasize the great variations occurring normally in bone marrow cell counts on healthy individuals. It is therefore important to bear in mind that a finding on one cell, deviating from the average, does not necessarily constitute pathology, but merely indicates the need for repeated counts and for further investigation in an attempt to establish a diagnosis. It is much more important to consider the total bone marrow pattern and the numerical relationship of all cells to each other in order to arrive at a diagnosis rather than to base conclusions on the deviation of one cell from the normal.

One must further consider that variations in individual counts due to uneven distribution of bone marrow elements within the bone marrow cavity or on the slide are reduced by aspirating a larger amount of bone marrow as well as by centrifugation and mixture of the material. Direct smears will be influenced more by uneven distribution of the marrow, however, the dilution factor will enter to a lesser degree.

This study, by presenting the normal bone marrow pattern, may be of assistance in judging pathologic conditions of the bone marrow. However, the numerical study of the bone marrow pattern, while aiding materially in the establishment of a diagnosis, is no substitute for the morphologic examination of the bone marrow cells, the examination of the blood and the clinical evaluation of the patient's condition.

Summary and Conclusion

The bone marrow of 151 normal infants, children and young adults ranging in age from birth to 20 years was studied. The data were statistically evaluated and recorded in table and graph form. The following observations were made:

1. The height of the various layers in the centrifuged specimen as obtained by aspiration of 1 cc. or fraction thereof of marrow fluid was compared in the different age groups and showed an increase with progressing age of the fat and myeloid-erythroid cell layers and a decrease of the mature red cell layer.

2. The cellular composition of the bone marrow varies with age.

3. Marked variations occur during the first year of life and particularly during the first month. Thereafter up to the end of the observation period the changes are of minor extent and average values for this age group were established for all cells.

4. The cells of the erythroid series show a sharp decrease in number during the first days of life and reach essentially stable values (23.12%) by the end of the first month with a temporary decrease around the third month of life.

5. The myeloid series shows an increasing during the first two weeks of life followed

by a sharp drop around the third week and the establishment by the end of the first month of values close to the average percentage as calculated for the period from 1 to 20 years (60.59%).

6. The lymphocytes increase in number during the first weeks of life, followed by a gradual decrease during the first and second year and thereafter do not show marked variations in number. (Average: 16.03%.)

7. The individual cells of the myeloid and erythroid series show a pattern similar to the one described for the entire series of which they are part. There is, however, a tendency for the younger cells to slightly decrease in number and the older cells to increase with advancing age. Numerical variations with age on cells occurring in smaller numbers are less noticeable than on cell groups occurring in higher percentages.

8. The myeloid-erythroid ratio is the expression of the numerical relationship of the myeloid and erythroid series. The values are low at birth, increase rapidly during the first two weeks and approach the 1 to 20 year average (2.95) during the first year.

9. The data reported in the literature were recorded in order to complement and compare the findings of this study.

10. The normal bone marrow pattern as described may contribute to the interpretation of the cellular composition of the bone marrow under abnormal conditions. However, the diagnostic significance of individual cell findings may be limited by the great variations occurring normally in the cellular composition of the bone marrow of healthy individuals.

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BOOK REVIEWS

PRINCIPLES AND PRACTICES OF THERAPEUTIC EXERCISES, by Hans Kraus, M.D., Springfield, Ill., Charles C Thomas, Publisher, 1949, $6.50, 336 pp., 290 illustrations. Fabrikoid.

In the field of physical medicine there is need for a book which will outline the principles underlying therapeutic exercise, and which will give definite examples of their clinical application. The physiologic foundation for many of the clinical applications of exercises is not too firm, so that a book which would be able to relate the principles of exercise to the fundamental underlying physiologic principles would be a most valuable one. The author attempts to do this in the first part of this book, which is called "Fundamental Working Principles." Although his presentations are clear and concise, they leave much to be desired in terms of definition, terminology and physiologic basis. Thus, the term "zero cerebral muscle" to indicate the overstretched and weak antagonist to a spastic muscle is a misleading term. The definitions of spasm, spasticity, hypertenseness and rigidity would not satisfy Sherrington or any of the more modern neurophysiologists. In spite of these criticisms, however, the book has been well organized and does offer a great deal of information in a logical manner which would help to clarify the thinking of the neophyte in this subject.

The author is definitely partial to certain forms of therapy, as iontophoresis of novocaine and the use of the ethyl chloride spray in overcoming trigger points, and undue emphasis is given to these subjects.

The portion of the book dealing with the application of therapeutic exercises to specific clinical problems is perhaps the most important part of the book, since specific exercises are prescribed and illustrated. This portion is somewhat weak in its diagnostic descriptions of the various specific diseases, particularly in discussion of upper motor neuron lesions. Here, too, the use of such terms as "confusion motions," to indicate synkinetic or re-enforcing motions, is confusing.

The illustrations in the book are clear, although often placed too far from the references in the text. The bibliography, though far from complete, indicates that the author has spent much time in reading on the subject. The sections having to do with exercises for musculo-skeletal conditions are perhaps the most authoritative and most valuable parts of the book.

The book would be most valuable to physicians, students and therapists, but would be of less value as a text for physiatrists.

MALNUTRITION AND STARVATION IN WESTERN NETHERLANDS—September 1944 to July 1945, Editorial Committee: Dr. G. C. E. Burger (Netherlands), Lieut. Col. H. R. Sandstead (U.S.A. and Canada), Sir J. C. Drummond (Great Britain), The Hague, General State Printing Office, 1948; Part I: 187 pp., 70 figures; Part II: Appendices, 299 pp.

The history of malnutrition and starvation in Holland during World War II is told in vivid manner in this 2-volume report. What can happen to a normally well-fed population under the conditions of ruthless control of Nazi occupation and the lessons learned in the relief of the resulting starvation are described in well-documented detail. The early chapters review the deterioration of health and the food situation during occupation. The depletion of farm produce and the large exports to Germany brought Holland to a state of starvation which became most severe in the Western areas in the winter of 1944-45, when the Allied forces were fighting their way up from Southern Holland, just before liberation. It was at this time that Allied nutrition experts laid elaborate plans for rushing survey teams and special nutrients to the areas of distress as soon as they were freed. Of particular interest to the pediatrician is the fact that even among the most severely starved people specific vitamin deficiencies were rare, while hunger edema was prevalent. Also of particular interest was the experience with protein hydrolysates. Oral and intravenous preparations of these hydrolysates were made available in large quantities on the theory that severely starved persons would be able to assimilate only these predigested foods. Actually, however, it was clearly shown that such predigested foods are not essential for resuscitating patients, even in the last stages of exhaustion from starvation.

The report, with its tabulated and graphic data contained in the Appendices in Part II, makes a significant contribution to our knowledge of nutrition and should prove of further value if, unhappily, it should again prove necessary to assist on a large scale victims of another famine.

MITCHELL'S PEDIATRICS AND PEDIATRIC NURSING, ed. 3, Robert A. Lyon, M.D., and Elgie M. Wallinger, R.N., B.S., M.A., Philadelphia, W. B. Saunders Company, 1949, $3.75, 590 pp.

In this third revision Dr. Lyon has again been assisted by Miss Elgie Wallinger, who was his co-author in the first edition. It is a text and reference for student nurses. The excellent arrangement of the book has been retained. As before, there are units dealing with growth and development, the child in the home, in the hospital and in the community, as well as units on nutrition, abnormalities and diseases. Most of the illustrations and tabulations are unchanged. They are well-chosen and serve to clarify and amplify the text. References at the end of each unit are adequate, although a more comprehensive inclusion of recent articles and books would have strengthened the bibliography. Unfortunately, a few books have been listed in their early editions. Suggestions for a collection of visual aids have been added. An outline for instruction, which comes as a separate booklet, should prove valuable for the teacher in nursing of children.

The section dealing with emotional and social development has been expanded and improved. The chapter on mental growth and development has been rewritten and is a concise and careful exposition of the concept that there is the same sequence of development in all children but that the rate of growth is variable and is attained at an individual pace. Progress is considered within the family framework; emphasis is placed on the part that parents play in stimulating performance and mental growth in their children, in furnishing normal outlets for emotional desires, and in guiding them into normal social relationships.

Most suggestions for the management of children in the hospital situation are psychologically sound and are discussed in a practical enough manner to enable the student nurse to apply them effectively. In isolated instances, however, suggestions for the handling of problems of behaviour do not conform to the general tone of the book. One example, on how to cope with the refusal of food, advises the nurse to give the child miniature servings and as these are taken to gradually increase the amount as his progress warrants it. The text states: "There is to be no feeding at all between meals and no mercy if the child asks for more than has been apportioned for that meal. Negativism of the adult will overcome negativism of the child." This inflexible point of view is not typical; nevertheless, it is unfortunate that it has survived in the present revision.

For the most part, the unit on diseases of children has been brought up to date. An extensive range of subjects has been covered; the result is sometimes a rather superficial treatment of certain important diseases and an inclusion of others which logically belong in a larger pediatric reference book. Thus, conditions such as epidemic diarrhea of the newborn infant and erythroblastosis fetalis would benefit by more detailed discussion, whereas malaria and tularemia could be eliminated. New subject matter, which includes cardiovascular surgery and current procedures in neurosurgery, merits consideration. Knowledge and skills in these areas are now sufficiently established to warrant inclusion in a textbook and are essential to the nurse who faces increasing demands to give intelligent care to such patients.

The approach to the discussion of diseases is the traditional one of dealing primarily with the physical aspects of diagnosis and treatment. Psychologic implications in such a disorder as chronic ulcerative colitis are not mentioned. Since the average nurse is likely to find herself at a loss in the field of psychosomatic medicine, she requires more information and guidance than has been provided. The growth of psychiatric services for children in the community and in the hospital and their contribution to better understanding and better handling of children, though inferred, might well have been reinforced by the citing of specific programs and activities.

Miss Rena M. Gazeway has contributed a new chapter on the responsibility of the community in health promotion and disease prevention. She outlines the role of the public health nurse as a health teacher and her functions in providing generalized service to the family with particular attention to the mental as well as the physical well-being of the child. There is, however, no account of the important part played by the Children's Bureau in maternal and child welfare, and the references to community resources are limited in scope. Problems of rehabilitation in chronic conditions also need further elaboration.

In most respects, this book should be an exceedingly useful reference for the student of pediatric nursing. It provides an excellent basis for understanding the well child and for meeting his emotional and physical needs during sickness and health.